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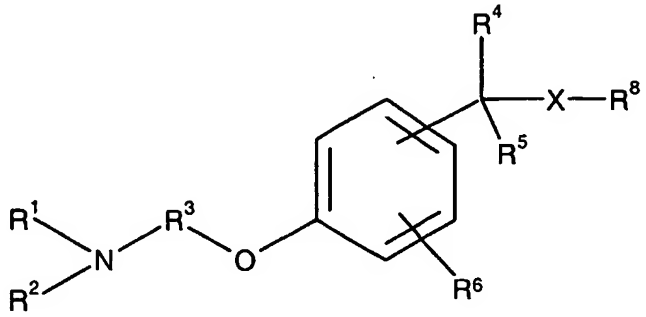
[Continued on next page]

(54) Title: NON-IMIDAZOLE ARYL ALKYLAMINES COMPOUNDS AS HISTAMINE H3 RECEPTOR ANTAGONISTS, PREPARATION AND THERAPEUTIC USES



(I)

(57) Abstract: The present invention discloses novel substituted aryl alkylamine compounds of Formula (I) or pharmaceutically acceptable salts thereofwhich have selective histamine-H3 receptor antagonist activity as well as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising such cyclic amines as well as methods of using them to treat obesity and other histamine H3 receptor -related diseases.

WO 02/076925 A2

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NON-IMIDAZOLE ARYL ALKYLAMINES COMPOUNDS AS HISTAMINE H3 RECEPTOR ANTAGONISTS, PREPARATION AND THERAPEUTIC USES

BACKGROUND OF THE INVENTION

The present invention relates to histamine H3 receptor antagonists, and as such are useful in the treatment of disorders responsive to the inactivation of histamine H3 receptors, such as obesity, cognitive disorders, attention deficient disorders and the like.

The histamine H3 receptor (H3R) is a presynaptic autoreceptor and hetero-receptor found in the peripheral and central nervous system and regulates the release of histamine and other neurotransmitters, such as serotonin and acetylcholine. The histamine H3 receptor is relatively neuron specific and inhibits the release of a number of monamines, including histamine. Selective antagonism of the histamine H3 receptor raises brain histamine levels and inhibits such activities as food consumption while minimizing non-specific peripheral consequences. Antagonists of the histamine H3 receptor increase synthesis and release of cerebral histamine and other monoamines. By this mechanism, they induce a prolonged wakefulness, improved cognitive function, reduction in food intake and normalization of vestibular reflexes. Accordingly, the histamine H3 receptor is an important target for new therapeutics in Alzheimer disease, mood and attention adjustments, cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness.

The majority of histamine H3 receptor antagonists to date resemble histamine in possessing an imidazole ring generally substituted in the 4(5) position (Ganellin et al., Ars Pharmaceutica, 1995, 36:3, 455-468). A variety of patents and patent applications directed to antagonists and agonists having such structures include EP 197840, EP 494010, WO 97/29092, WO 96/38141, and WO96/38142. These imidazole-containing compounds have the disadvantage of poor blood-brain barrier penetration, interaction with cytochrome P-450 proteins, and hepatic and ocular toxicities.

Non-imidazole neuroactive compounds such as beta histamines (Arrang, Eur. J. Pharm. 1985, 111:72-84) demonstrated some histamine H3 receptor activity but with poor potency. EP 978512 published March 1, 2000 discloses non-imidazole aryloxy

alkylamines discloses histamine H3 receptor antagonists but does not disclose the affinity, if any, of these antagonists for recently identified histamine receptor GPRv53, described below. EP 0982300A2 (pub. March 1, 2000) discloses non-imidazole alkyamines as histamine HS receptor ligand which are similar to the subject invention by having a phenoxy core structure although the subject invention is unique in the dissimilar substitutions at the ortho, meta or para positions of the central benzene ring, the exact substitutions of the non-oxygen benzene ring substituent, and in some cases the presence of a saturated, fused heterocyclic ring appended to the central benzene core. Furthermore the compounds of this invention are highly selective for the H3 receptor (vs. other histamine receptors), and possess remarkable drug disposition properties (pharmacokinetics).

Histamine mediates its activity via four receptor subtypes, H1R, H2R, H3R and a newly identified receptor designated GPRv53 [(Oda T., *et al.*, J.Biol.Chem. 275 (47): 36781-6 (2000)]. Although relatively selective ligands have been developed for H1R, H2R and H3R, few specific ligands have been developed that can distinguish H3R from GPRv53. GPRv53 is a widely distributed receptor found at high levels in human leukocytes. Activation or inhibition of this receptor could result in undesirable side effects when targeting antagonism of the H3R receptor. Furthermore, the identification of this new receptor has fundamentally changed histamine biology and must be considered in the development of histamine H3 receptor antagonists.

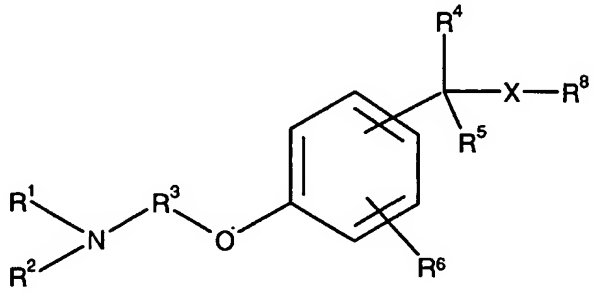
Because of the unresolved deficiencies of the compounds described above, there is a continuing need for improved methods and compositions to treat disorders associated with histamine H3 receptors.

The present invention provides compounds that are useful as histamine H3 receptor antagonists. In another aspect, the present invention provides compounds that are useful as selective antagonists of the histamine H3 receptor but have little or no binding affinity of GPRv53. In yet another aspect, the present invention provides pharmaceutical compositions comprising antagonists of the histamine H3 receptor.

In yet another aspect, the present invention provides compounds, pharmaceutical compositions, and methods useful in the treatment of obesity, cognitive disorders, attention deficient disorders and other disorders associated with histamine H3 receptor.

SUMMARY OF THE INVENTION

The present invention is a compound structurally represented by Formula I



or pharmaceutically acceptable salts thereof wherein:

X is O, NR^7 or S;

R^1 is hydrogen,

C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,

$(CHR^5)_n$-C_3-C_7 cycloalkyl,

$(CHR^5)_n$ aryl,

$(CHR^5)_n$ heteroaryl, or

$(CHR^5)_n$-$O(CHR^5)_n$-aryl;

R^2 is independently R^1, or

COR^1 , or cyclized with the attached nitrogen atom at the R^1 position to form a 4, 5, or 6 member carbon ring, wherein one of said carbons is optionally replaced by one of O, S, NR^1 or CO, or wherein the ring formed by R^1 and R^2 is optionally substituted one to two times with C_1-C_4 alkyl;

R^3 is independently C_3-C_7 cycloalkylene, or C_1- C_4 alkylene optionally substituted;

R^4 is hydrogen,

halogen,

C_1-C_4 alkyl,

$(CHR^5)_n$-C_3-C_7 cycloalkyl,

$(CHR^5)_n$ aryl,

$(CHR^5)_n$ heteroaryl,

$(CHR^5)_n$-$O(CHR^5)_n$-aryl or

CO or

cyclized with R^5 to from a cyclopropyl ring;

R^5 is hydrogen , or

C_1-C_4 alkyl;

R^6 is hydrogen,

halo or

cyclized with the attached carbon atom at the R^5 position to form a 5 to 6 member carbon ring,

cyclized with the attached carbon atom at the R^7 position to form a 5 to 6 member heterocyclic ring or

R^7 is hydrogen,

C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,

$(CHR^5)_n$-C_3-C_7 cycloalkyl,

$(CHR^5)_n$ aryl,

$(CHR^5)_n$ heteroaryl,

$(CHR^5)_n$-$O(CHR^5)_n$-aryl,

SO_2R^1 or

Cyclized with attached carbon on R^8 to from a 5, 6, or 7 membered carbon ring optionally substituted with R^9, CF_3, or CN, optionally one of the said carbons is replaced by N, NR^1, CO;

R^8 is hydrogen,
a bond,
C_1-C_8 alkyl
$-SO_2 R^9$,
$-CO_2 R^{10}$,
$-CO R^9$,
$-CONH R^{10}$;

R^9 is hydrogen,
halogen,
C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,
C_3-C_7 cycloalkyl,
aryl,
CH_2 aryl,
heteroaryl,
heterocycle,
$-O(CHR^5)_n$-aryl,
$-COR^1$,
$-CONR^1 R^2$,
$-SO_2R^1$,
$-OR^1$,
$-N(R^1)_2$,
$-NR^1 R^2$,
$-CH_2NR^1 R^2$,

-$CONR^1R^2$

-$NHSO_2R^1$,

-NO_2,

-CO_2R^1,

-$SO_2N(R^1)_2$,

-$S(O)_nR^1$,

-OCF_3,

-CH2SR[5],

R^{10} is hydrogen,

halogen,

C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,

C_3-C_7 cycloalkyl,

aryl,

CH_2 aryl,

heteroaryl,

heterocycle,

-COR^1,

-$CONR^1R^2$,

-SO_2R^1,

-$N(R^1)_2$,

-NR^1R^2,

-$CH_2NR^1R^2$,

-$CONR^1R^2$

-CO_2R^1,

-$SO_2N(R^1)_2$,

-$S(O)_nR^1$,

-CH2SR[5],

and n is 0 - 4.

In preferred embodiments of Formula I the core phenoxy ring is an o, m, or p-disubstituted benzene, more preferably a p-disubstituted benzene. In alternative embodiments R^6 forms a bicyclic carbon ring at the R^5 position. Alternatively, R^6 may form a bicyclic heterocyclic ring at the R^7 position. Preferably, X is nitrogen, R^4 and R^5 are independently H or CH_3, R1 and R2 are independently a C_1-C_8 alkyl and R9 is a di-C_1 to C_2 alkyl-amino.

The present invention is a pharmaceutical composition which comprises a compound of Formula I and a pharmaceutically acceptable carrier. Pharmaceutical formulations of Formula I can provide a method of selectively increasing histamine levels in cells by contacting the cells with an antagonist of the histamine H3 receptor, the antagonists being a compound of Formula I.

The present invention further provides an antagonist of Formula I which is characterized by having little or no binding affinity for the histamine receptor GPRv53. Thus, a pharmaceutical preparation of Formula I can be useful in the treatment or prevention of obesity, cognitive disorders, attention deficient disorders and the like, which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Formula I. In addition, a pharmaceutical preparation of Formula I can be useful in the treatment or prevention of a disorder or disease in which inhibition of the histamine H3 receptor has a beneficial effect or the treatment or prevention of eating disorders which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

Throughout the instant application, the following terms have the indicated meanings:

The term "GPRv53" means a recently identified novel histamine receptor as described in Oda, *et al., supra*. Alternative names for this receptor are PORT3 or H4R.

The term "H3R" means to the histamine H3 receptor that inhibits the release of a number of monoamines, including histamine.

The term "H1R" means to the histamine H1 receptor subtype.

The term "H2R" means to the histamine H2 receptor subtype.

The term "selective H3R antagonists" is defined as the ability of a compound of the present invention to block forskolin-stimulated cAMP production in response to agonist R (-)α methylhistamine.

"Alkylene" are a saturated hydrocarbyldiyl radical of straight or branched configuration made up of from 1 to 4 carbon atoms. Included within the scope of this term are methylene, 1,2 –ethane-diyl, 1,1-ethane-diyl, 1,3-propane diyl, 1,2-propane diyl, 1,3 butane-diyl, 1,4 –butane diyl, and the like.

"C_3-C_7 cycloalkylene" are a saturated hydrocarbyldiyl radical of cyclic configuration, optionally branched, made up of from 3 to 7 carbon atoms. Included within the scope of this term are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the like.

"Alkyl" are one to four or one to eight carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric forms thereof.

"Aryl" are six to twelve carbon atoms such as phenyl, alpha -naphthyl, beta -naphthyl, m-methylphenyl, p-trifluoromethylphenyl and the like. The aryl groups can also be substituted with one to 3 hydroxy, fluoro, chloro, or bromo groups.

"Cycloalkyl" are three to seven carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

"Heteroaryl" are six to twelve carbon atoms aryls, as described above, containing the heteroatoms nitrogen, sulfur or oxygen. Heteroaryls are pyridine, thiophene, furan, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pryidazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl.

"Heterocycle" are three to twelve carbon atom cyclic aliphatic rings, wherein one or more carbon atoms is replaced by a hetero-atom which is nitrogen, sulfur or oxygen.

"Halogen" or "halo" means fluoro, chloro, bromo and iodo.

"Composition" means a pharmaceutical composition and is intended to encompass a pharmaceutical product comprising the active ingredient(s), Formula I, and the inert ingredient(s) that make up the carrier. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term "unit dosage form" means physically discrete units suitable as unitary dosages for human subjects and other non-human animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The terms "treating" and "treat", as used herein, include their generally accepted meanings, i.e., preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, described herein.

In one embodiment, the present invention provides compounds of Formula I as described in detail above. Another embodiments are where the phenoxy core structure is an o, m, or p- disubstituted aryl. Another embodiment is a compound wherein R^6 is cyclized with the attached carbon atom at R^7 to form, including the fused benzene ring, a substituted tetrahydroisoquinoline ring. Another embodiment is a compound wherein X is nitrogen, and wherein R^7 and R^8 are cyclized to form, together with X, a pyrrolidine ring, and wherein R^9 is –CH2-N-pyrrolidinyl.

A preferred moiety for X is independently O or N.

A preferred moiety for R^9 is C_1-C_8 dialkylamino. A more preferred embodiment is where the dialkylamino is dimethylamino.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutical salts, its enantiomers and racemic mixtures thereof.

Because certain compounds of the invention contain a basic moiety (e.g., amino), the compound of Formula I can exist as a pharmaceutical acid addition salt. Such salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-

hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, beta-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-l-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

As stated earlier, the invention includes tautomers, enantiomers and other stereoisomers of the compounds also. Thus, as one skilled in the art knows, certain aryls may exist in tautomeric forms. Such variations are contemplated to be within the scope of the invention.

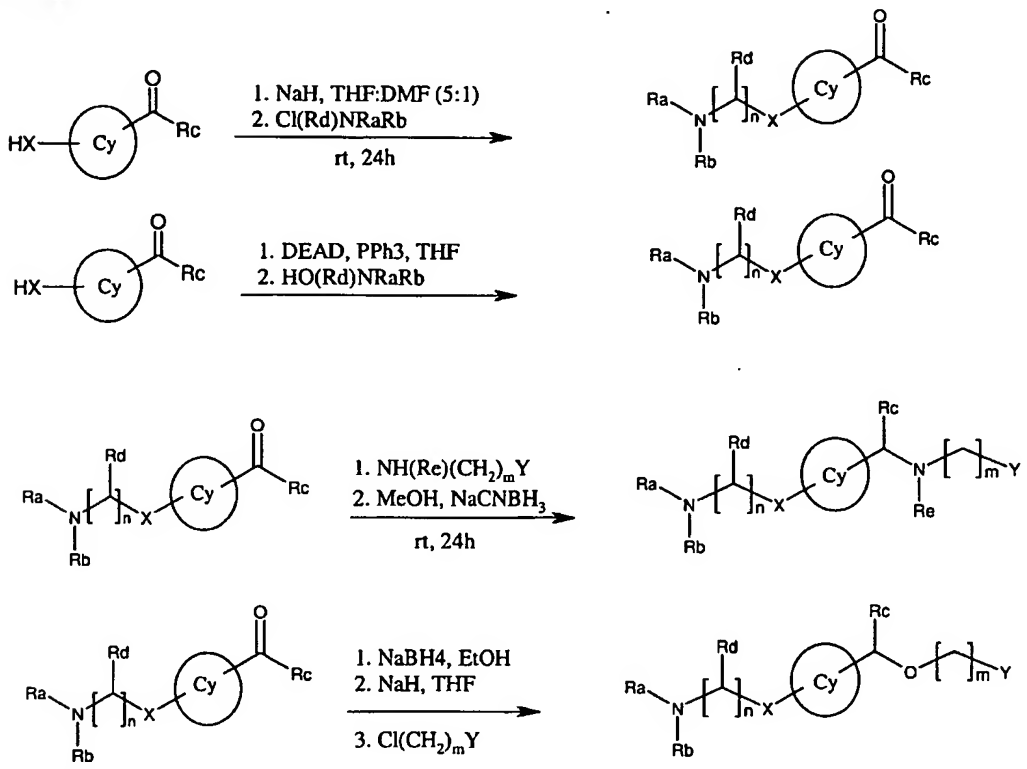
The compounds of Formula I may be prepared by several processes well known in the art. The compounds of the present invention are prepared by standard alkylation or Mitsunobu chemistries and reductive animations known to one skilled in the art, or by the methods provided herein, supplemented by methods known in the art. Generally, this reaction is conducted in an organic solvent such as, for example, halogenated hydrocarbons, toluene, acetonitrile and the like, preferably in the absence of moisture, at temperatures in the range about 0-100o C., by bringing together the ingredients in contact in the solvent medium and stirring for about 10 minutes to about 48 hours at such temperatures.

The compounds of Formula I, when existing as a diastereomeric mixture, may be separated into diastereomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Alternatively, any enantiomer of a compound of the formula may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration or through enantioselective synthesis.

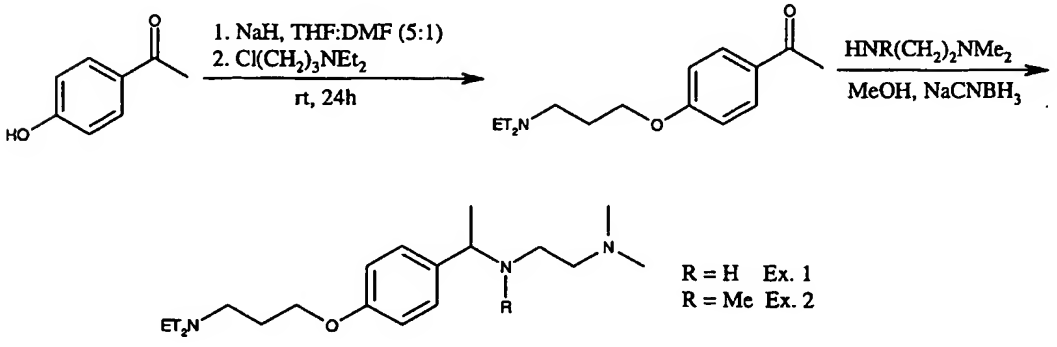
The Examples shown in Table 1 below are being provided to further illustrate the present invention. They are for illustrative purposes only; the scope of the invention is

not to be considered limited in any way thereby. The preparation of compounds of Formula I, are depicted in the schemes and procedures below.

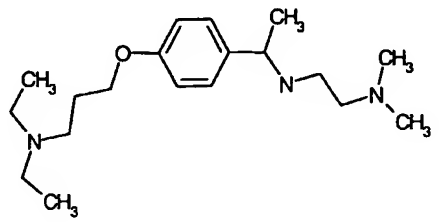
Scheme 1.



Scheme 2



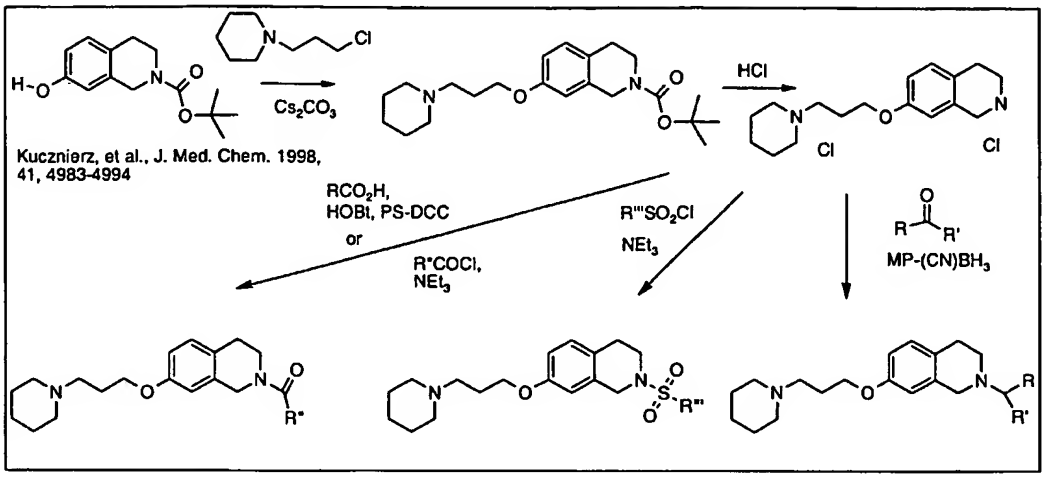
Preparation of N-{1-[4-(3-Dimethylamino-propoxy)-phenyl-N',N'-dimethyl-ethane-1,2-diamine

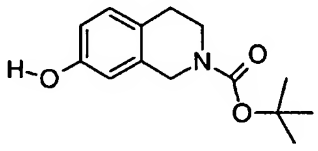


Example 2

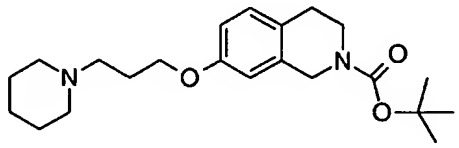
To a 100 mL round-bottom flask was placed NaH (60% dispersion, 38.4 mg, 1.0 mmol) and anhydrous THF (10 mL, 0.1 M) under an atmosphere of nitrogen. Then, a DMF solution of p-hydroxyacetophenone (62 mg, 0.5 mmol) was added at 0 C. After 15 minutes, a DMF solution of 3-chloro-N,N-diethyl-N-proplyamine (150 mg, 1.0 mmol) was added, and the reaction was allowed to slowly reach room temperature over 3 hours. The reaction was then quenched with water, diluted with ether and washed with water (3 x 20 mL) and brine (2x 20 mL). Concentration *in vacuo* afforded 114 mg (92%) of an off-white solid. LCMS indicated a purity of 95% and hit the mass, 249.1. This material was then dissolved in ethanol (4 mL, 0.1M) and 1-N, N-dimethylamino-2-N-methylaminoethane (114 mg, 0.45 mmol) was added. After 15 minutes at room temperature, $NaCNBH_3$ (56 mg, 0.9 mmol) was added and the reaction was allowed to stir overnight at room temperature. The reaction was then with water, diluted with ether and washed with water (3 x 20 mL) and brine (2x 20 mL). Concentration *in vacuo* afforded 134 mg (93%) of an orange oil. Column chromatography (9:1, CH_2Cl_2:MeOH) afforded an orange oil. LCMS indicated a purity of 99% and hit the mass, 321.2.

7-OH tetrahydroisoquinoline series





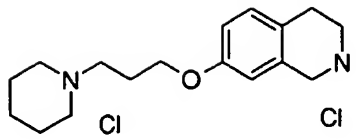
7-Hydroxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester is prepared by the procedure described in Kucznierz, et.al., J. Med. Chem. 1998, 41, 4983-4994. MS(ES-) 248.1 $(M-H)^-$.



Example 228

7-(3-Piperidin-1-yl-propoxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester;

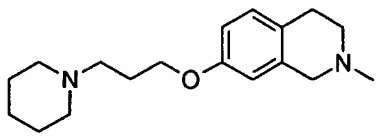
Procedure A: A 100 mL dioxane solution of 7-hydroxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester (5.0 g, 20 mmol) is stirred under N_2 as Cs_2CO_3 (13.3 g, 43 mmol), KI (0.1 g, 0.6 mmol), then N-(3-chloropropyl)piperidine (3.9 g, 24 mmol) are added in succession. The reaction mixture is heated at 90°C for 10 hours, cooled, filtered, and concentrated to give the crude product. Purification by chromatography (SiO_2; 0-10% MeOH/CH_2Cl_2/1%NH_4OH gradient) gives the product as an amber oil (7.5 g, 100% yield). MS(ES+)375.3$(M+H)^+$.



Example 238

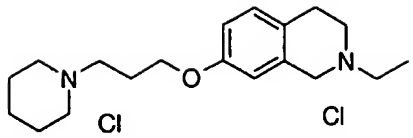
7-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride;

Procedure B: A 50 mL CH_2Cl_2 solution of 7-(3-Piperidin-1-yl-propoxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester (5.1 g, 13.8 mmol) is stirred under N_2 at 0-10°C as 4N HCl/dioxane (11.5 mL, 46 mmol) is added dropwise. After the addition is complete, reaction mixture is stirred at this temperature for 30-60 min, then allowed to warm to room temperature. A white precipitate forms and dry MeOH is added until clear solution is obtained. Additional 4N HCl/dioxane (11.0 mL, 44 mmol) is added dropwise. After the addition is complete, reaction mixture is stirred at room temperature. Reaction is followed by TLC (SiO_2 plate, $CH_3Cl/MeOH/NH_4OH$; 25/5/1) until starting material consumed (4-5 h). Reaction mixture is concentrated, dissolved in dry MeOH, concentrated, triturated in Et_2O, filtered, and dried *in vacuo* to give the di-HCl salt (4.5 g, 94% yield) as a white solid. MS(ES+)275.3$(M+H)^+$free base.



Example 245

2-Methyl-7-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: A 10 mL THF suspension of LAH (150 mg,4 mmol) is stirred under N_2 at 0-10°C as a 10 mL THF solution of 7-(3-piperidin-1-yl-propoxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester (200 mg, 0.53 mmol) is added dropwise. Reaction mixture is allowed to warm to room temperature, refluxed 90 minutes, cooled to 0-10°C, quenched with H_2O and 15% aqueous NaOH, filtered, and the filtrate concentrated to give crude product. Material is purified by chromatography (SiO_2; 0-10% $MeOH/CH_2Cl_2/1\%NH_4OH$ gradient)to give the product (82 mg, 54% yld). MS(ES+)289.1$(M+H)^+$.

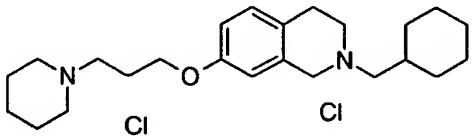


Example 271

2-Ethyl-7-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride;

Procedure C: An 80 mL CH_2Cl_2/MeOH (9:1) solution of 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (658972)(2.95 g, 8.5mmol) is stirred under N_2, the MP-$CNBH_3$ resin(15 g, 38 mmol) added, the acetaldehyde (5 mL, 89 mmol) added, the pH is adjusted to ~4 with glacial AcOH and reaction mixture stirred at room temperature for 18-20 hours. The reaction mixture is filtered and the resin beads washed twice alternately with MeOH, then CH_2Cl_2. The filtrate is concentrated and the residue is purified by chromatography (SCX-MeOH wash, elute 2M NH_3/MeOH; then (SiO_2; 0-10% MeOH/CH_2Cl_2/1%NH_4OH gradient) to give the pure free base.

Procedure D: A 50 mL THF/MeOH (1:1) solution of the free base (1.52 g, 5 mmol) is stirred under N_2 at 0-10°C as 1N HCl/Et_2O (11.5 mL, 11.5 mmol) is added dropwise. After the addition is complete, reaction mixture is allowed to warm to room temperature, then reaction mixture is concentrated, dissolved in dry MeOH, concentrated, triturated in Et_2O, filtered, and dried *in vacuo* to give the di-HCl salt (4.5 g, 94% yld) as a white solid. MS(ES+)303.3$(M+H)^+$ free base.

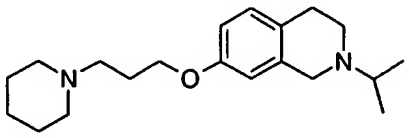


Example 292 (di-HCL salt)

Example 273 (free base)

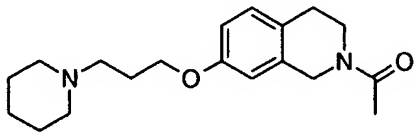
2-Cyclohexylmethyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride: 2-Cyclohexylmethyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (6 g, 17 mmol), MP-$CNBH_3$ (30 g, 76.5 mmol), and cyclohexanecarboxaldehyde (12.4 mL, 102 mmol) via a procedure substantially analogous to Procedure C except that the SCX column is not used in purification. The di-

HCl salt product (4.9 g, 65% yld) is isolated as a white solid via a procedure substantially analogous to Procedure D. MS(ES+)371.4$(M+H)^+$free base.



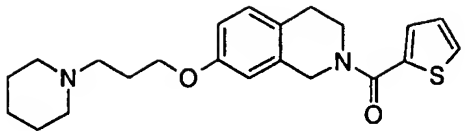
Example 244

2-Isopropyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: 2-Isopropyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (520 mg, 1.5 mmol), MP-$CNBH_3$ (3.2 g, 7.5 mmol), and acetone (1.1 mL, 15 mmol) via a procedure substantially analogous to Procedure C except that the SCX column is not used in purification. The product (210 mg, 44% yld) is isolated as a clear oil. MS(ES+)317.2$(M+H)^+$.



Example 275

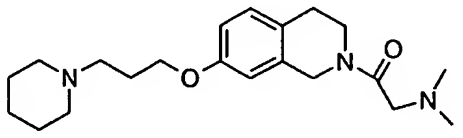
1-[7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone: A 5 mL CH_2Cl_2 solution of 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol) and NEt_3 (0.25 mL, 1.7 mmol) is stirred under N_2, a 1 mL CH_2Cl_2 solution of acetyl chloride (0.043 mL, 0.6 mmol) is added, and reaction is stirred at room temp. for 5-6 hours. Reaction mixture is quenched with MeOH, concentrated and the residue is purified by chromatography (SCX-MeOH wash, elute 2M NH_3/MeOH; then (SiO_2; 0-10% MeOH/CH_2Cl_2/1%NH_4OH gradient) to give the product (90 mg, 58% yld). MS(ES+)317.1$(M+H)^+$



Example 257

[7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiophen-2-yl-methanone;

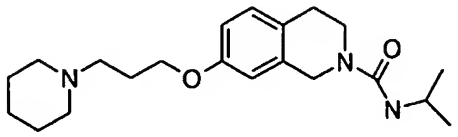
Procedure E: A 7 mL $CHCl_3$/*t*-BuOH/MeCN (5:1:1) mixture of 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (256 mg, 0.74 mmol), resin bound DCC (1.1 g, 0.9 mmol), hydroxybenzotriazole (HOBt, 150 mg, 1.1 mmol), and thiophene-2-carboxylic acid (118 mg, 0.9 mmol) is shaken in a capped vial at room temperature for 48 hours. The reaction mixture is filtered and the resin beads washed twice alternately with MeOH, then CH_2Cl_2. The filtrate is concentrated and the residue is purified by chromatography (SCX-MeOH wash, elute 2M NH_3/MeOH; then SiO_2; 0-10% MeOH/CH_2Cl_2/1% NH_4OH gradient) to give the pure free base as a solid (180 mg, 63% yld). MS(ES+) 385.1$(M+H)^+$. A 3 mL dry MeOH solution of the free base (45 mg, 0.12 mmol) is stirred with 1N HCl/Et_2O (0.18 mL, 0.18 mmol) for 5 minutes, concentrated, triturated with Et_2O, filtered, and dried *in vacuo* to the HCl salt as an off-white solid (46 mg). MS(ES+) 385.1$(M+H)^+$free base.



Example 274

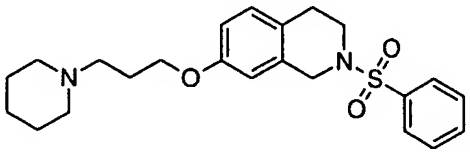
2-Dimethylamino-1-[7-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone: 2-Dimethylamino-1-[7-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol), PS-DCC (800 mg, 1.1 mmol), HOBt (80 mg, 0.77 mmol), NEt_3 (0.21 mL, 1.5 mmol)and N,N-dimethylglycine (1.1 mL, 15 mmol) via a procedure substantially analogous to Procedure E except that PS-trisamine resin beads (700 mg, 2.6 mmol) is used in the work up to scavenge the excess HOBt and

N,N-dimethylglycine. The free base product (35 mg, 19% yld) is isolated as an oil. MS(ES+)360.5$(M+H)^+$.



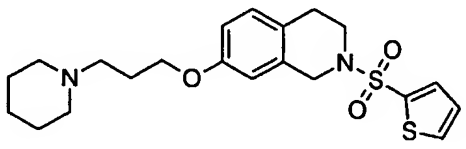
Example 266

7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropylamide: A 10 mL CH_2Cl_2 solution of 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (254 mg, 0.73 mmol), NEt_3 (0.20 mL, 1.4 mmol), isopropyl isocyanate (192 mg, 2.2 mmol), and 4-dimethylaminopyridine (12 mg, 0.1 mmol) is stirred under N_2, at room temperature for 18 hours. The reaction mixture is concentrated and the residue is purified by chromatography (SCX-MeOH wash, elute 2M NH3/MeOH; then SiO_2; 0-10% MeOH/CH_2Cl_2/1%NH_4OH gradient) to give pure product (110 mg, 42% yld). MS(ES+) 360.2$(M+H)^+$.



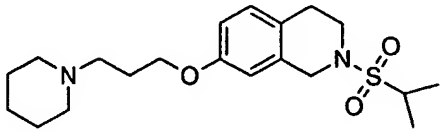
Example 249

2-Benzenesulfonyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline; **Procedure F:** A 5 mL CH_2Cl_2 solution of 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (185 mg, 0.53 mmol) and NEt_3 (0.22 mL,1.8 mmol) is stirred under N_2, benzenesulfonyl chloride (0.08 mL, 0.62 mmol) is added, and reaction is stirred at room temperature for 5-6 hours. Reaction mixture is diluted with EtOAc, washed with saturated aqueous Na_2CO_3, and the aqueous layer back-extracted with EtOAc. The EtOAc extracts are combined, dried (Na_2SO_4), and concentrated. The residue is purified by chromatography (SiO_2; 0-6% MeOH/CH_2Cl_2/1% NH_4OH gradient) to give the product (160 mg, 73% yld). MS(ES+) 415.1$(M+H)^+$.



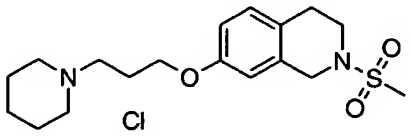
Example 268

7-(3-Piperidin-1-yl-propoxy)-2-(thiophene-2-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline: 7-(3-Piperidin-1-yl-propoxy)-2-(thiophene-2-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol), NEt_3 (0.25 mL, 1.8 mmol), and thiophene-2-sulfonyl chloride (114 mg, 0.63 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the product (160 mg, 76% yld). MS(ES+)421.1$(M+H)^+$.



Example 267

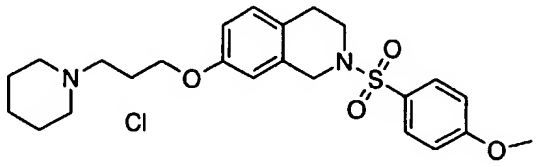
7-(3-Piperidin-1-yl-propoxy)-2-(propane-2-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline: 7-(3-Piperidin-1-yl-propoxy)-2-(propane-2-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol), NEt_3 (0.25 mL, 1.8 mmol), and isopropylsulfonyl chloride (0.07 mL, 0.60 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the product (93 mg, 49% yld). MS(ES+) 381.1$(M+H)^+$.



Example 284

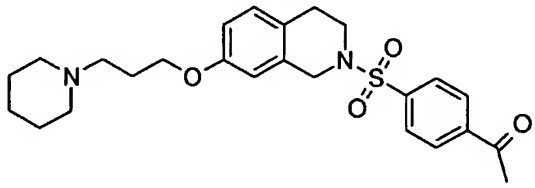
2-Methanesulfonyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride: 2-Methanesulfonyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (183 mg, 0.52 mmol), NEt_3 (0.25 mL, 1.8 mmol), and methanelsulfonyl chloride (0.05 mL, 0.66 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the free base product. A 5 mL dry MeOH solution of the free base (110 mg, 0.31 mmol) is stirred with 1N HCl/Et_2O (0.50 mL, 0.5 mmol) for 5 minutes,

concentrated, triturated with Et_2O, the Et_2O decanted, and the residue dried *in vacuo* to give the HCl salt as a glass (118 mg, 65% yld). MS(ES+) 353.2$(M+H)^+$free base.



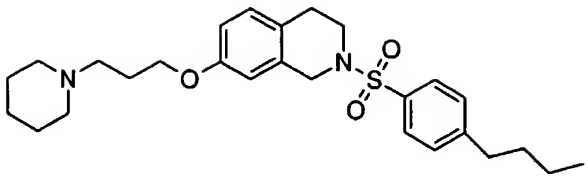
Example 286

2-(4-Methoxy-benzenesulfonyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride: 2-(4-Methoxy-benzenesulfonyl-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (150 mg, 0.43 mmol), NEt_3 (0.21 mL, 1.5 mmol), and 4-methoxybenzenesulfonyl chloride (115 mg, 0.57 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the free base product. A 5 mL dry MeOH solution of the free base (131 mg, 0.29 mmol) is stirred with 1N HCl/Et_2O (0.40 mL, 0.4 mmol) for 5 minutes, concentrated, triturated with Et_2O, filtered, and dried *in vacuo* to give the HCl salt (118 mg, 57% yld). MS(ES+) 445.2$(M+H)^+$free base.



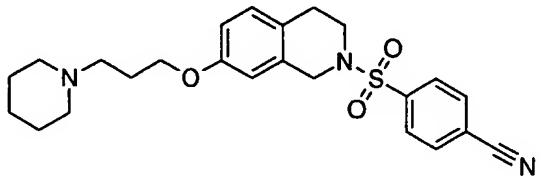
Example 277

1-{4-[7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-sulfonyl]-phenyl}-ethanone: 1-{4-[7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-sulfonyl]-phenyl}-ethanone is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol), NEt_3 (0.25 mL, 1.8 mmol), and 4-acetylbenzenelsulfonyl chloride (131 mg, 0.60 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the product (85 mg, 37% yld). MS(ES+) 457.1$(M+H)^+$.



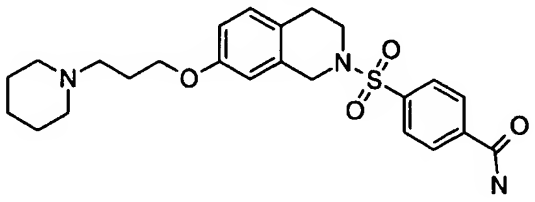
Example 276

2-(4-n-Butyl-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: 2-(4-n-Butyl-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol), NEt_3 (0.25 mL, 1.8 mmol), and 4-(*n*-butyl)benzenesulfonyl chloride (140 mg, 0.60 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the product (165 mg, 70% yld). MS(ES+)471.1$(M+H)^+$.



Example 278

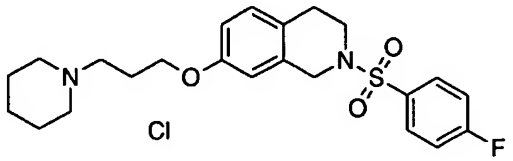
2-(4-Cyanobenzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: 2-(4-Cyanobenzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.5 mmol), NEt_3 (0.25 mL, 1.8 mmol), and 4-cyanobenzenesulfonyl chloride (121 mg, 0.60 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the product (157 mg, 71% yld). MS(ES+) 440.1$(M+H)^+$.



Example 287

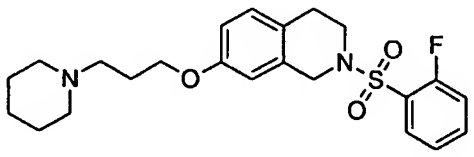
4-[7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-sulfonyl]- benzamide: A 1.4 mL DMSO mixture of K_2CO_3 is stirred under N_2, 2-(4-cyanobenzenesulfonyl)-7-(3-

piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline (75 mg, 0.17 mmol) is added, 0.2 mL H_2O added, followed by 30% H_2O_2 (1.4 mL, 12 mmol) and reaction is stirred at room temperature for 4 hours. The reaction mixture is diluted with MeOH, filtered, and the solids washed twice with MeOH. The filtrate is concentrated and the residue is purified by chromatography (SCX-MeOH wash, elute 2M NH_3/MeOH; then SiO_2; 0-10% MeOH/CH_2Cl_2/1%NH_4OH gradient) to give the product as an off-white solid (26 mg, 26% yld). MS (ES+)458.2$(M+H)^+$.



Example 285

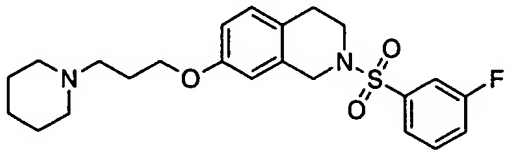
2-(4-Fluoro-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride: 2-(4-Fluoro-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (158 mg, 0.45 mmol), NEt_3 (0.21 mL, 1.5 mmol), and 4-fluorobenzenesulfonyl chloride (115 mg, 0.55 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give 140 mg of free base product. The free base is converted to the HCl salt (150 mg, 71% yld) via a procedure substantially analogous Procedure D. MS (ES+)433.2$(M+H)^+$free base.



Example 304

2-(2-Fluoro-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: 2-(2-Fluoro-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (104 mg, 0.3 mmol), NEt_3 (0.14 mL, 1.1 mmol), and 2-fluorobenzenesulfonyl chloride (80 mg, 0.41 mmol) via a procedure substantially

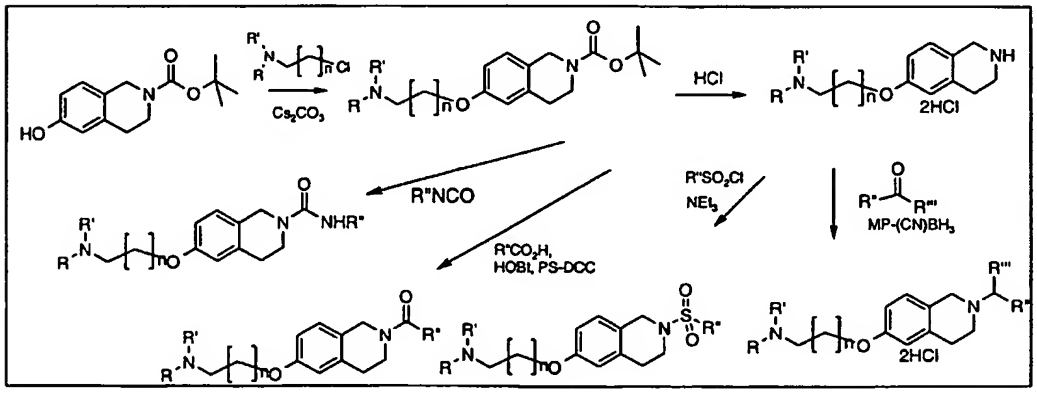
analogous to Procedure F except that an additional SCX column purification step is performed to give the free base product (85 mg, 66% yld) as an amber oil. MS (ES+) 433.2(M+H)$^+$.

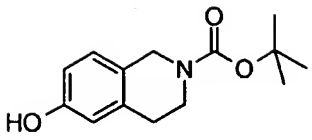


Example 305

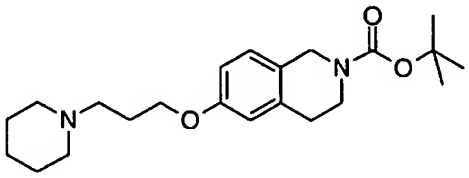
2-(3-Fluoro-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: 2-(3-Fluoro-benzenesulfonyl)-7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 7-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (104 mg, 0.3 mmol), NEt_3 (0.14 mL, 1.1 mmol), and 3-fluorobenzenesulfonyl chloride (80 mg, 0.41 mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the free base product (90 mg, 70% yld) as an off-white solid. MS (ES+) 433.2(M+H)$^+$.

6-OH tetrahydroisoquinoline series





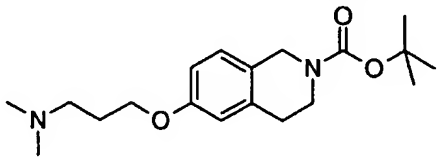
6-hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester is prepared by the procedures similar to those described in Selnick, H.G.; Smith, G. R.; Tebben, A. J.; *Synth.Commun.* 1995, *25*, 3255-3262.



Example 127

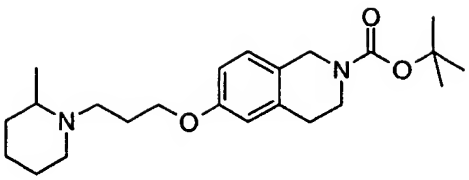
6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester: To a round-bottom flask, equipped with stir bar and septum, is placed 6-hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (1 g, 4.01 mmol), KI (599 mg, 4.01 mmol) and NaH (162 mg, 95%dry, 6.42 mmol). Then, dry DMF (20 mL, 0.5 M) is added via syringe followed by N-(3-chloropropyl)piperidine (0.85 mL, 5.2 mmol). The reaction is allowed to stir at 70 degrees overnight. In the morning, the reaction is quenched with water, extracted into EtOAc (3 x 20 mL) and dried over brine. Column chromatography in 9:1 DCM:MeOH affords 6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester an orange oil (1 g, 67%). Mass sec hit M+1, 375; LCMS >95% @ 230 nm and ELSD.

In a similar manner the Examples 35, 139, and 164 are prepared:



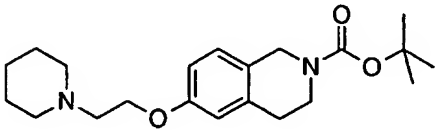
Example 35

6-(3-Dimethylamino-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester; M+1 335



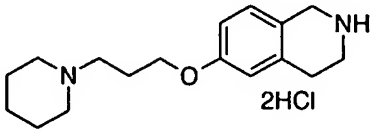
Example 139

6-[3-(2-Methyl-piperidin-1-yl)-propoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester; M+1 389



Example 164

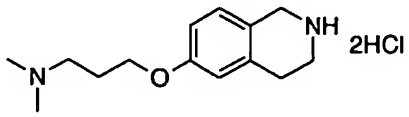
6-(2-Piperidin-1-yl-ethoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester; M+1 361.



Example 128

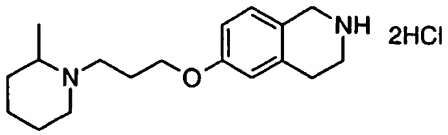
6-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride: To a round-bottom flask, equipped with stir bar and septum, is placed 6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (1 g, 2.6 mmol), DCM (20 mL) and 4M HCl/dioxane (5 mL). The reaction is allowed to stir at room temperature for 3 h. After this time, the reaction is concentrated, dissolved in MeOH and concentrated again affording 6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride as a white solid (800 mg, 87%). Mass spec hit M+1, 275; LCMS >95% @ 230 nm and ELSD.

In a similar manner the Examples 40, 140, and 165 are prepared:



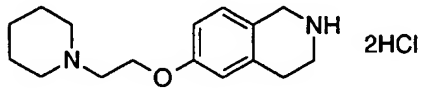
Example 40

Dimethyl-[3-(1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-propyl]-amine dihydrochloride; M+1 235.



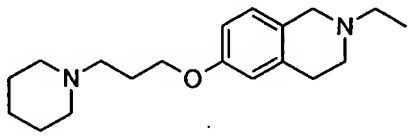
Example 140

6-[3-(2-Methyl-piperidin-1-yl)-propoxy]-1,2,3,4-tetrahydro-isoquinoline dihydrochloride; M+1 289.



Example 165

6-(2-Piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride; M+1 261.

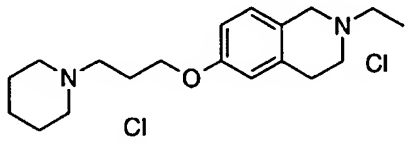


Example 129

2-Ethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: To a 25 mL round-bottom flask is placed 6-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (700 mg, 2.01 mol), MP-$CNBH_3$ (2.5 g, 6.05 mmol, 2.42 mmol/g) and DCM/MeOH (9mL/1mL). Then, acetaldehyde is added (0.7 mL, 12 mmol) and the reaction is allowed to stir overnight. The reaction is then filtered, washed with DCM/MeOH and concentrated. Column chromatography in 9:1 DCM:MeOH affords 2-ethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline (493 mg, 71%) of a viscous oil. Mass spec hit M+1, 303; LCMS >95% @ 230 nm and ELSD. Array synthesis followed this general procedure in 4 mL vials to make the following compounds:

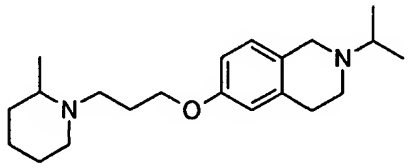
Example	Name	MS
76	[3-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-propyl]-dimethyl-amine	263
77	{3-[6-(3-Dimethylamino-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propyl}-dimethyl-amine	320
80	2-[6-(3-Dimethylamino-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-acetamide	292
81	Dimethyl-{3-[2-(2-piperidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-propyl}-amine	346
82	Dimethyl-[3-(2-pyridin-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-propyl]-amine	326
83	Dimethyl-[3-(2-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-propyl]-amine	326
141	2-Ethyl-6-[3-(2-methyl-piperidin-1-yl)-propoxy]-1,2,3,4-tetrahydro-isoquinoline	317
145	2-Cyclopropylmethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline	329
146	2-Cyclopentylmethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline	357
147	2-Cyclohexylmethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline	371
148	2-(2-Ethyl-butyl)-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline	359
149	6-(3-Piperidin-1-yl-propoxy)-2-propyl-1,2,3,4-tetrahydro-isoquinoline	317
166	2-Ethyl-6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline	289

169	2-Cyclopropylmethyl-6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline	315
170	2-Cyclopentylmethyl-6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline	343
171	2-Cyclohexylmethyl-6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline	357
172	2-(2-Ethyl-butyl)-6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline	345
168	2-Isopropyl-6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-isoquinoline	303



Example 250

2-Ethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride: 2-Ethyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline (5.12g, 16.9 mmol) is dissolved in MeOH (50 mL), and 1M HCl in ether is added dropwise (37.2 mL, 37.2 mmol) and the mixture is stirred for 10 minutes and concentrated to give the dihydrochloride salt as a white solid (6.0 g, 93%).

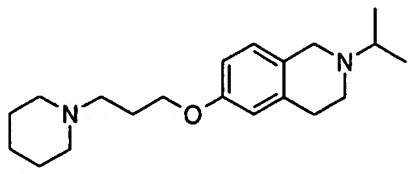


Example 143

2-Isopropyl-6-[3-(2-methyl-piperidin-1-yl)-propoxy]-1,2,3,4-tetrahydro-isoquinoline: To a flask equipped with a stir bar is placed 6-[3-(2-Methyl-piperidin-1-yl)-propoxy]-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (300 mg, 0.83 mmol), acetone (excess), $NaCNBH_3$ (155 mg, 2.5 mmol) in MeOH (8 mL) and the mixture stirred at room temperature for 2h. The reaction mixture is diluted with water, and extracted with

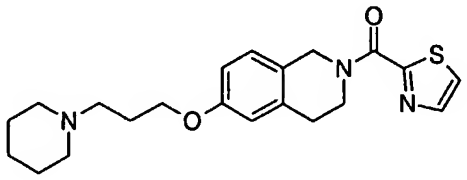
CH_2Cl_2. The organic phase is dried over Na_2SO_4 and concentrated. M+1 331, LCMS >98% @ 230 nm and ELSD.

In a similar manner Example 138 is prepared:



Example 138

2-Isopropyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline; M+1 317, LCMS 100% @ 230 nm and ELSD.



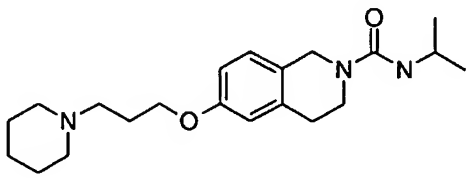
Example 162

[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiazol-2-yl-methanone: To a 4 mL vial is placed 6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (28 mg, 0.08 mmol), resin-bound DCC (134 mg, 0.16 mmol, 1.2 mmol/g), HOBt (16 mg, 0.12 mmol), pyrazole carboxylic acid (13 mg, 0.1 mmol) and a 5:1:1 mixture of $CHCl_3$:CH_3CN:tBuOH. The vial is agitated by means of a lab quake shaker overnight. In the morning, PS-trisamine (134 mg, 0.4 mmol, 3.0 mmol/g) is added and the reaction is again allowed to rotate overnight to scavenge excess carboxylic acid and HOBt. Filtration, washing with DCM/MeOH and concentration affords a orange foam. Filtration through a short pipet column provides 24 mg (80%) of [6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiazol-2-yl-methanone as an orange solid. Mass spec hit M+1, 386; LCMS >95% @ 230 nm and ELSD. Array synthesis follows this general procedure in 4 mL vials to make the following examples:

Example	Name	MS
78	[6-(3-Dimethylamino-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(1-phenyl-5-trifluoromethyl-1H-pyrazol-4-yl)-methanone	474

134	1-[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone	315
156	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(tetrahydro-furan-2-yl)-methanone	386
157	(5-Methyl-furan-2-yl)-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	383
158	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(1H-pyrrol-2-yl)-methanone	368
159	2-Methylsulfanyl-1-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone	363
160	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiophen-2-yl-methanone	385
161	N,N-Dimethyl-4-oxo-4-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-butyramide	402
162	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiazol-2-yl-methanone	386
163	5-[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carbonyl]-pyrrolidin-2-one	386
175	2-Dimethylamino-1-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone	360
176	(1-Methyl-pyrrolidin-2-yl)-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	386
177	2-Dimethylamino-1-[6-(2-piperidin-1-yl-ethoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone	346
182	1-[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propan-1-one	332
183	Cyclopropyl-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	344
184	Cyclobutyl-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	358

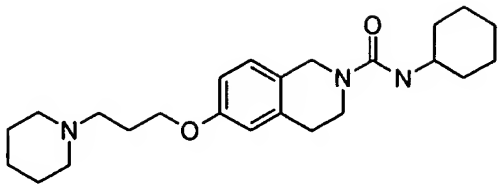
185	Cyclopentyl-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	372
186	2-Methyl-1-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-propan-1-one	346
187	Cyclohexyl-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	385
188	2-Ethyl-1-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-butan-1-one	373
193	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-pyridin-4-yl-methanone	381
194	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-pyridin-3-yl-methanone	381
195	[6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-pyridin-2-yl-methanone	381
196	Isoxazol-5-yl-[6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone	371



Example 178

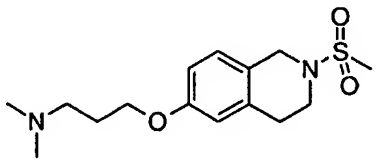
6-(2-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropylamide: To a 4 mL vial is placed 6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (25.0 mg, 0.07 mmol), resin-bound Hunigs base (81 mg, 0.29 mmol, 3.54 mmol/g), resin bound DMAP (catalytic), and dry CH_2Cl_2 and isopropyl isocyanate (16 □L, 0.18 mmol). The vial is agitated by means of a lab quake shaker overnight. In the morning, PS-trisamine (120 mg, 0.36 mmol, 3.0 mmol/g) is added and the reaction again allowed to rotate for 4 hours to scavenge excess isocyanate. Filtration, washing with CH_2Cl_2 and concentration afforded the desired urea. M+1 360.

In a similar manner Examples 179 is prepared:



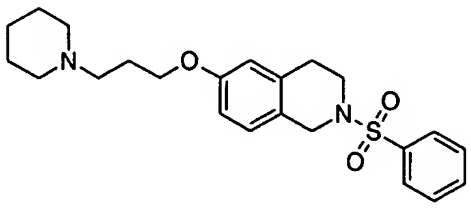
Example 179

6-(2-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid cyclohexylamide; M+1 400.



Example 79

[3-(2-Methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-propyl]-dimethyl-amine: To a 4 mL vial is placed Dimethyl-[3-(1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-propyl]-amine (24.0 mg, 0.1 mmol), resin-bound DIEA (58 mg, 0.2 mmol, 3.54 mmol/g), MsCl (12 □L, 0.15 mmol) and dry CH_2Cl_2 (2 mL). The vial is allowed to rotate overnight. In the morning, PS-trisamine (136 mg, 0.41 mmol, 3.0 mmol/g) is added and the reaction again allowed to rotate for 4 hours to scavenge excess MsCl. Filtration, washing with CH_2Cl_2 and concentration affords the desired urea LCMS >99% @ 230 nm and ELSD, M+1 360.

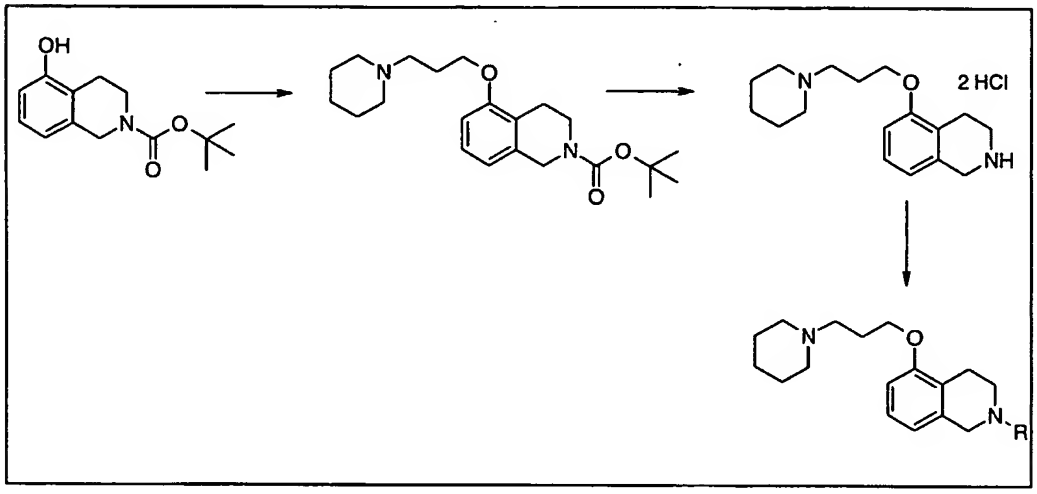


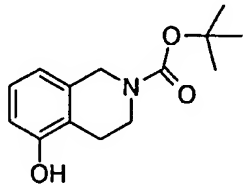
Example 302

2-Benzenesulfonyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline: 2-Benzenesulfonyl-6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (330 mg, 0.95 mmol), NEt_3 (0.48 mL, 3.5 mmol), and benzenesulfonyl chloride (0.15 mL, 1.17

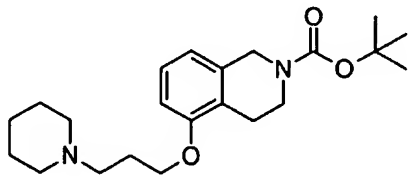
mmol) via a procedure substantially analogous to Procedure F except that an additional SCX column purification step is performed to give the product as a white solid (250 mg, 63% yld). MS(ES+) 415.3$(M+H)^+$.

5-OH tetrahydroisoquinoline series





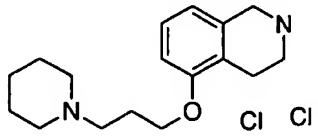
5-Hydroxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester is prepared by the procedures similar to those described in Durand S.; Lusinchi, X.; Moreau, R. C. *Bull. Soc. Chim. France* 1961, *207*, 270; and Georgian, V.; Harrison, R. J.; Skaletzky, L. L.; *J Org Chem* 1962, *27*, 4571.



Example 290

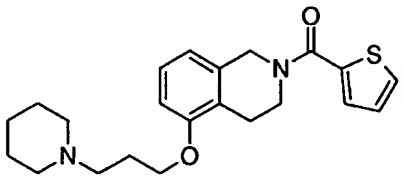
5-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester is prepared from 5-Hydroxy-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester (5.69 g, 22.8 mmol) in a manner substantially analogous to Procedure A

except DMF is used in place of dioxane. Following aqueous workup, the crude material is purified by flash chromatography [Biotage 65M SiO_2, elute 10% (25/5/1 $CHCl_3$/MeOH/NH_4OH) / 90% (10% MeOH/$CHCl_3$)] to give the title compound (5.2 g, 61%). MS (ES+) 375.3



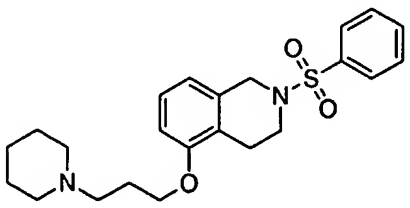
Example 291

5-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt is prepared from 5-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (4.0 g, 10.7 mmol) in a manner substantially analogous to Procedure B to give the title compound as an off-white solid (3.47 g, 93%). MS (ES+) 275.2



Example 309

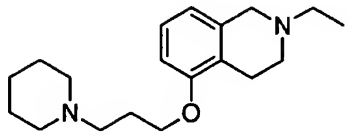
[5-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiophen-2-yl-methanone is prepared from 5-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (0.256 g, 0.74 mmol) in a manner substantially analogous to Procedure E to give the title compound as an off-white solid (0.109 g, 38%). MS (ES+) 415.2



Example 294

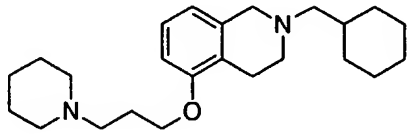
2-Benzenesulfonyl-5-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 5-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (150 mg, 0.43 mmol) via a procedure substantially analogous to

Procedure F to provide the title compound as an off-white solid (54 mg, 30%). MS (ES+) 385.2



Example 306

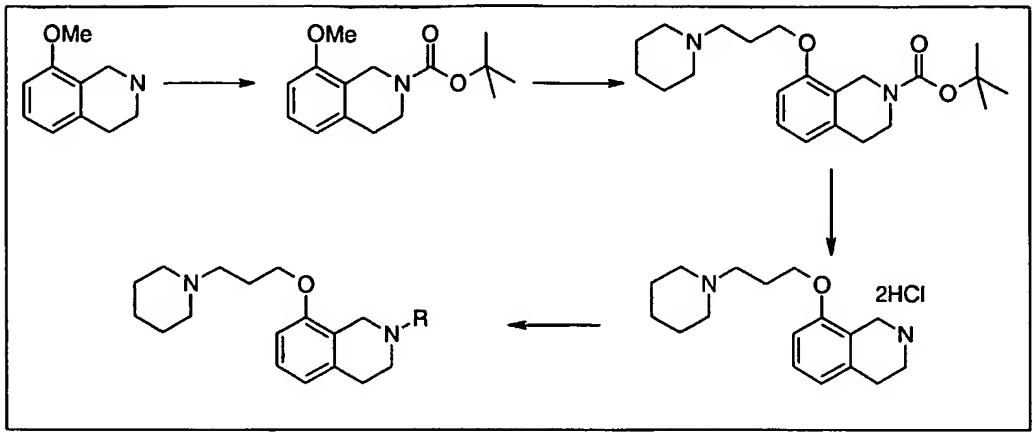
2-Ethyl-5-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 5-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (375 mg, 1.1 mmol) in a manner substantially analogous to Procedure C to give the title compound as a yellow oil (49 mg, 15%). MS (ES+) 303.3

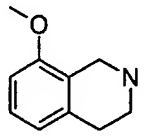


Example 313

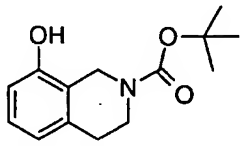
2-Cyclohexylmethyl-5-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 5-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (350 mg, 1.0 mmol) in a manner substantially analogous to Procedure C to give the title compound as a yellow oil (0.142 mg, 38%). MS (ES+) 371.4

8-OH tetrahydroisoquinoline series



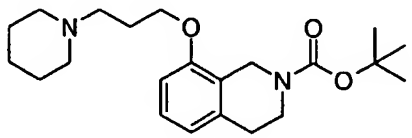


8-Methoxy-1,2,3,4-tetrahydro-isoquinoline is prepared according to Shanker, P. S.; Subba Rao, G. S. R. *Indian J. of Chemistry section B* 1993, 32B, 1209-1213.



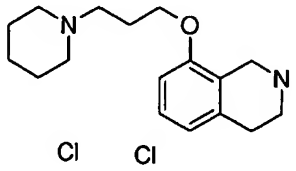
8-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester: To a mixture of 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (2.54 g, 15.6 mmol) in CH_2Cl_2 (60 mL) at –78 °C is added a solution of boron tribromide in CH_2Cl_2 (1 M, 52 mL, 52 mmol) dropwise over approximately 20 minutes. The cooling bath is removed, and the mixture is warmed to room temperature. After 4 h, the reaction is carefully quenched with ice. EtOAc and water is added, and the mixture is stirred overnight. The phases are separated, and 5 N NaOH solution is added to the aqueous phase until pH is basic. Dioxane (250 mL) and di-*tert*-butyl dicarbonate (6.78 g, 31 mmol) is added, and reaction mixture is stirred at room temperature overnight. EtOAc is added, and the phases are separated. The aqueous phase is extracted with EtOAc (1X), and the combined organic phase is washed with

brine and dried ($MgSO_4$). After filtration, the solvent is removed *in vacuo* to provide the title compound (4.84 g) that is used without purification. MS (ES-) 248.2.



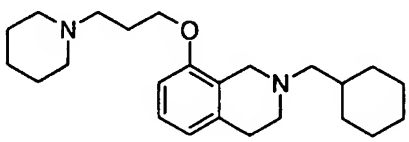
Example 307

8-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester is prepared from 8-hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (0.84 g, 3.4 mmol) in a manner substantially analogous to Procedure A except DMF is used in place of dioxane. Following aqueous workup, the crude material is purified by chromatography [SCX-MeOH wash, elute 2M NH_3/MeOH then Biotage 40s SiO_2, elute 10% (25/5/1 $CHCl_3$/MeOH/NH_4OH) / 90% (10% MeOH/$CHCl_3$)] to give the title compound (0.61 g, 48%). MS (ES+) 375.3.



Example 308

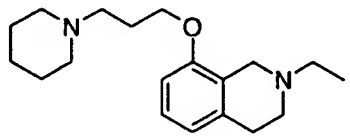
8-(3-Piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt is prepared from 8-(3-piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (3.09 g, 8.25 mmol) in a manner substantially analogous to Procedure B to give the title compound as an off-white solid (2.63 g, 85%). MS (ES+) 275.3



Example 309

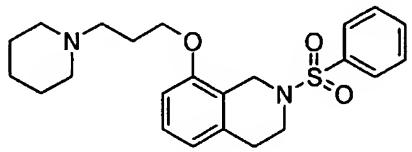
2-Cyclohexylmethyl-8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline

dihydrochloride salt (0.375 g, 1.1 mmol) in a manner substantially analogous to Procedure C to give the title compound as a yellow oil (0.195 g, 48%). MS (ES+) 371.4



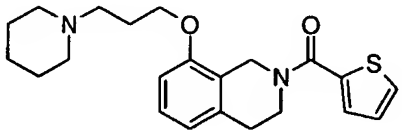
Example 310

2-Ethyl-8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (0.375 g, 1.1 mmol) in a manner substantially analogous to Procedure C to give the title compound as a yellow oil (0.124 g, 37%). MS (ES+) 303.3.



Example 311

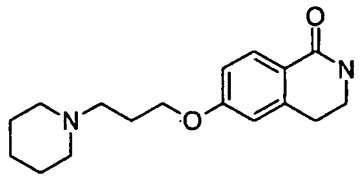
2-Benzenesulfonyl-8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline is prepared from 8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (300 mg, 0.86 mmol) via a procedure substantially analogous to Procedure F to provide the title compound as an off-white solid (0.22 g, 63%). MS (ES+) 415.3.



Example 312

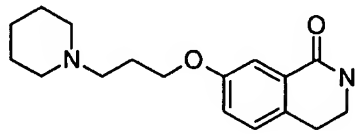
[8-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-1H-isoquinolin-2-yl]-thiophen-2-yl-methanone: To a mixture of 8-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride salt (300 mg, 0.86 mmol) and NEt_3 (0.36 mL, 2.6 mmol) in CH_2Cl_2 (10 mL) is added 2-thiophene carbonyl chloride (0.10 mL, 0.95 mmol). After stirring at room temperature overnight, the mixture is partitioned between EtOAc and water. The organic phase is washed with brine, dried ($MgSO_4$), and concentrated. The residue is purified by

flash chromatography [Biotage 40S SiO_2, elute 20% (90/10/1 CH_2Cl_2/MeOH/NH_4OH) / 80% CH_2Cl_2 to 100% (90/10/1 CH_2Cl_2/MeOH/NH_4OH)] to yield the title compound as a yellow oil (0.181 g, 55%). MS (ES+) 385.3.



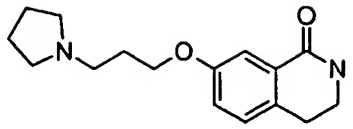
Example 206

6-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-2H-isoquinolin-1-one is prepared from 6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (CAS Registry Number 22245-98-3) (0.5 g, 2.9 mmol) in a manner substantially analogous to Procedure A except DMF is used in place of dioxane. Following aqueous workup, the crude material is purified by flash chromatography (Biotage 40M SiO_2, elute 90/10/1 CH_2Cl_2/MeOH/NH_4OH) to give the title compound as a white solid (0.516 g, 61%). MS (ES+) 289.1



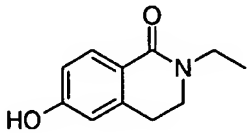
Example 207

7-(3-Piperidin-1-yl-propoxy)-3,4-dihydro-2H-isoquinolin-1-one is prepared from 7-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (CAS Registry Number 22246-05-5) (1.43 g, 8.76 mmol) in a manner substantially analogous to Procedure A except DMF is used in place of dioxane. Following aqueous workup, the crude material is purified by flash chromatography (Biotage 40M SiO_2, elute 90/10/1 CH_2Cl_2/MeOH/NH_4OH) to give the title compound as a white solid (1.11 g, 44%). MS (ES+) 289.1



Example 205

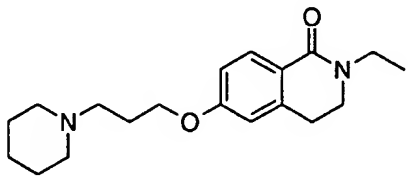
7-(3-Pyrrolidin-1-yl-propoxy)-3,4-dihydro-2H-isoquinolin-1-one is prepared from 7-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (0.48 g, 2.94 mmol) in a manner substantially analogous to Procedure A except DMF is used in place of dioxane and 1-(3-Chloro-propyl)-pyrrolidine is used instead of N-(3-chloropropyl)piperidine. Following aqueous workup, the crude material is purified by flash chromatography (Biotage 40M SiO_2, elute 90/10/1 CH_2Cl_2/MeOH/NH_4OH) to give the title compound as an off-white solid (0.17 g, 21%). MS (ES+) 275.1



2-Ethyl-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one:

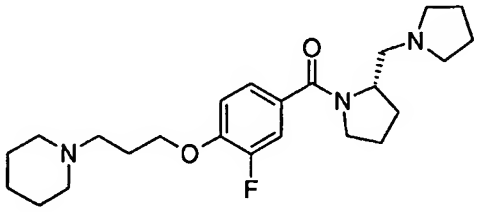
To a mixture of 6-methoxy-3,4-dihydro-2H-isoquinolin-1-one (0.30 g, 1.69 mmol) in THF (10 mL) is added sodium hydride (60% mineral oil suspension, 100 mg). The suspension is heated at reflux for 1 h, and cooled to room temperature. Ethyl iodide (1.4 mL, 17 mmol) is added, and the mixture is stirred at room temperature overnight. The mixture is partitioned between EtOAc and water. After the aqueous phase is extracted with EtOAc (2x), the combined organic phase is washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue is purified by flash chromatography (Biotage 40M SiO_2, elute 45% EtOAc:hexane – 50% EtOAc:hexane, linear gradient) to yield 2-ethyl-6-methoxy-3,4-dihydro-2H-isoquinolin-1-one as a colorless oil (0.275 g, 78%). The material is dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C. To the cooled mixture is added a solution of boron tribromide (1 M, 4.7 mL, 4.7 mmol) in CH_2Cl_2. After 0.5 h, the temperature is warmed to 0 °C and stirred for 3 h. After the reaction is carefully quenched with ice, EtOAc and water is added, and the mixture is vigorously stirred overnight. The phases are separated, and the organic phase is extracted with EtOAc (2x). The combined organic phase is washed with brine and dried ($MgSO_4$). The solvent is removed *in vacuo*, and the residue is purified by chromatography (Varian 10 g SiO_2

cartridge, elute 60% EtOAc:hexane) to provide 2-ethyl-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (0.209 g, 82%). MS (ES+) 192.0



Example 265

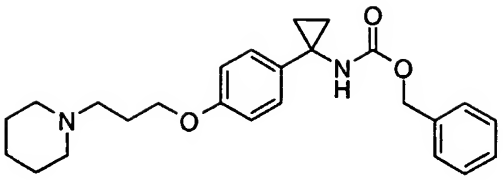
2-Ethyl-6-(3-piperidin-1-yl-propoxy)-3,4-dihydro-2H-isoquinolin-1-one is prepared from 2-Ethyl-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (0.192 g, 1.0 mmol) in a manner substantially analogous to Procedure A except DMF is used in place of dioxane. Following aqueous workup, the crude material is purified by chromatography [Varian 10 g SiO_2 cartridge, elute 10% (25/5/1 CHCl3/MeOH/NH_4OH) / 90% (10% MeOH/$CHCl_3$)] to obtain the title compound as a waxy off-white solid (77 mg, 24%). MS (ES+) 317.1



Example 303

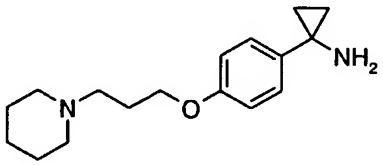
[3-Fluoro-4-(3-piperidin-1-yl-propoxy)-phenyl]-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone:

General Procedure G: A mixture of (3-Fluoro-4-hydroxy-phenyl)-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone (0.193 g, 0.66 mmol), Cs_2CO_3 (0.43 g, 1.32 mmol), KI (55 mg, 0.33 mmol), and N-(3-chloropropyl)piperidine (3.9 g, 24 mmol) in DMF (5 mL) is heated at 90 °C overnight. The mixture is partitioned between EtOAc and water. The phases are separated, and the aqueous phase is extracted with EtOAc (2x). The combined organic phase is washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue is purified by chromatography [SCX-MeOH wash, elute 2M NH_3/MeOH; then Biotage 12M SiO_2, elute 10% (25/5/1 $CHCl_3$/MeOH/NH_4OH) / 90% (10% MeOH/$CHCl_3$)] to give the title compound as a yellow oil (0.105 g, 38%). MS (ES+) 418.4



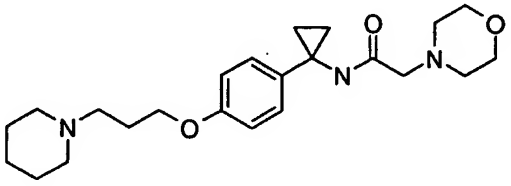
Example 240

{1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-cyclopropyl}-carbamic acid benzyl ester is prepared from [1-(4-Hydroxy-phenyl)-cyclopropyl]-carbamic acid benzyl ester (1.21 g, 4.28 mmol), Cs_2CO_3 (2.78 g, 8.55 mmol), KI (71 mg, 0.43 mmol), and N-(3-chloropropyl)piperidine (0.86 g, 5.34 mmol) in dioxane (50 mL) in a manner substantially analogous to Procedure A to give the product((1.16 g, 66%). MS (ES+) 409.3.



Example 241

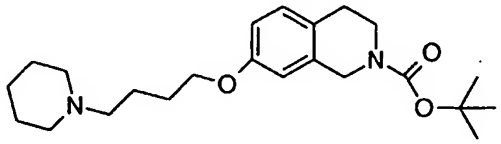
1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-cyclopropylamine: {1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-cyclopropyl}-carbamic acid benzyl ester (1.08 g, 2.65 mmol) is dissolved in ethanol (50 mL), and 10% Pd/C is added (200 mg). The mixture was stirred under a balloon on hydrogen for 3 hours. The reaction mixture was stirred through a plug of silica gel to give the desired compound. HRMS 275.2123 $(M+H)^+$.



Example 247

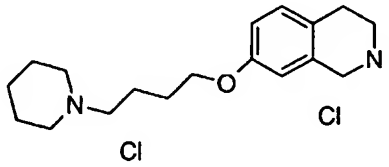
2-Morpholin-4-yl-N-{1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-cyclopropyl}-acetamide: 1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-cyclopropylamine (0.195 g, 0.72 mmol) and

morpholin-4-yl-acetic acid (0.125 g, 0.86 mmol) are dissolved in DMF, and diisopropylethylamine added (0.15 mL), followed by EDC (0.165 g, 0.86 mmol) and HOBt (0.116 g, 0.86 mmol). The reaction mixture was stirred overnight at room temperature. The residue is purified by chromatography [SCX-MeOH wash, elute 2M NH_3/MeOH; then Biotage 12M SiO_2, elute 10% (25/5/1 $CHCl_3$/MeOH/NH_4OH) / 90% (10% MeOH/$CHCl_3$)] to give the title compound as a yellow oil. HRMS 402.2765 $(M+H)^+$.



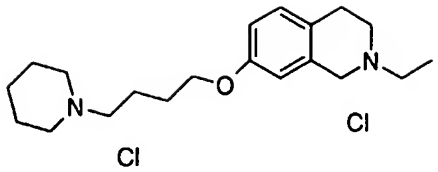
Example 316

7-(4-Piperidin-1-yl-butoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester: A 20 mL DMF mixture of 7-(4-chloro-butoxy)-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester(1.0 g, 3 mmol), piperidine (0.75 mL, 7.5 mmol), and KI (1.0 g, 6 mmol) is stirred at 50 °C under N_2 for four hours, then at room temperature for 16 hours. The reaction mixture is directly purified by chromatography (SCX-MeOH wash, elute 2M NH3/MeOH; then SiO_2; 0-6% MeOH/CH_2Cl_2/1%NH_4OH gradient)to give the free base (700 mg, 60% yld). MS(ES+)389.3 $(M+H)^+$free base.



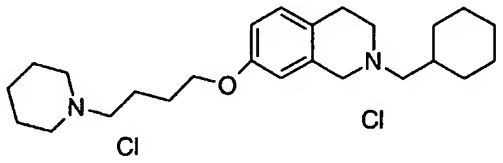
Example 314

7-(4-Piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride: 7-(4-Piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride is prepared from 7-(4-chloro-butoxy)-3,4-dihydro-1-H-isoquinoline-2-carboxylic acid tert-butyl ester(600 mg, 1.5 mmol) and 4N HCl/ dioxane (2.5 mL, 10 mmol) base in a manner substantially analogous to Procedure B to give the product(490 mg, 90% yld). MS(ES+)389.3 $(M+H)^+$free



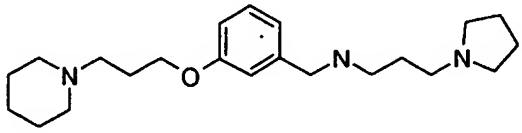
Example 315

2-Ethyl-7-(4-piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride: 2-Ethyl-7-(4-piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride is prepared from 7-(4-piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (252 mg, 0.7 mmol), and acetaldehyde (0.40 mL, 7 mmol) in a manner substantially analogous to Procedure C to give the dihydrochloride product as an off white solid(125 mg, 70% yld). MS(ES+)317.2$(M+H)^+$ free base.



Example 317

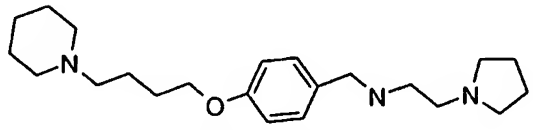
2-Cyclohexylmethyl-7-(4-piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride: 2-Cyclohexylmethyl-7-(4-piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride is prepared from 7-(4-piperidin-1-yl-butoxy)-1,2,3,4-tetrahydro-isoquinoline dihydrochloride (175 mg, 0.48 mmol), and cyclohexanecarboxaldehyde (0.35 mL, 2.9 mmol) in a manner substantially analogous to Procedure C to give the dihydrochloride product as an off white solid(105 mg, 62% yld). MS(ES+)385.3$(M+H)^+$ free base.



Example 208

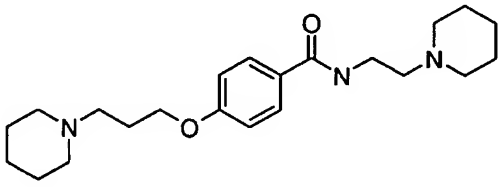
[3-(3-Piperidin-1-yl-propoxy)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amine: The reductive amination is run with 3-(3-piperidin-1-yl-propoxy)-benzaldehyde (1 g, 4 mmol) and), 3-

pyrrolridin-1-yl propylamine (1 mL, 8 mmol), and MP-$CNBH_3$ resin(4.5g, 10.4 mmol)via a procedure substantially analogous to [2-(3-piperidin-1-yl-propoxy)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amine to give the product as a yellow oil(818 mg, 58 % yld). MS(ES+)360.3$(M+H)^+$ free base.



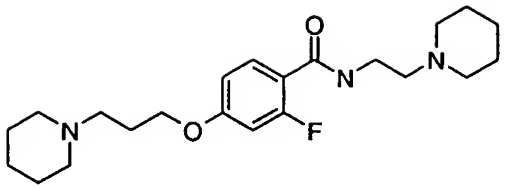
Example 202

[4-(4-Piperidin-1-yl-butoxy)-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amine: An 8 mL DMF solution of [4-(4-bromo-butoxy)-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amine (307 mg, 0.86 mmol) and piperidine (0.22 mL, 2.2 mmol) is stirred at 90 °C for six hours under N_2. The reaction mixture is cooled, diluted with CH_2Cl_2, filtered, washed with brine, dried (Na_2SO_4), and concentrated. The residue is purified by chromatography (SiO_2; 0-6% MeOH/CH_2Cl_2/1%NH_4OH gradient) to give the product (40 mg, 12% yld). MS(ES+)360.4$(M+H)^+$ free base.



Example 236

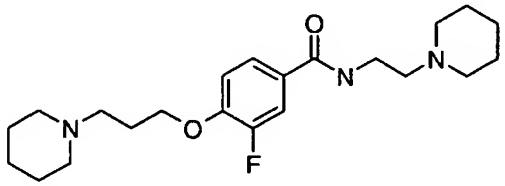
N-(2-Piperidin-1-yl-ethyl)-4-(3-piperidin-1-yl-propoxy)-benzamide is prepared according to general procedure A from 4-Hydroxy-N-(2-piperidin-1-yl-ethyl)-benzamide (CAS Registry 106018-38-6) (0.27 g, 1.1 mmol) to give the title compound as a white solid (77 mg, 19%). MS (ES+) 374.3



Example 237

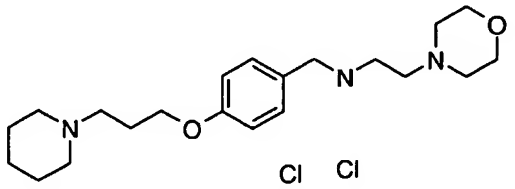
2-Fluoro-N-(2-piperidin-1-yl-ethyl)-4-(3-piperidin-1-yl-propoxy)-benzamide:

To a mixture of 2-Fluoro-4-(3-piperidin-1-yl-propoxy)-benzoic acid (70 mg, 0.25 mmol) and 1-(2-aminoethyl)piperidine (45 □L, 0.3 mmol) in DMF (5 mL) was added EDC (58 mg, 0.3 mmol), HOBT (40 mg, 0.3 mmol), and diisopropylethyl amine (52 □l, 0.3 mmol). The mixture was stirred at room temperature overnight. The mixture was partitioned between EtOAc and water. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (Biotage 12 M, elute 90/10/1 CH_2Cl_2/MeOH/NH_4OH) to yield the title compound. MS (ES+) 392.3



Example 264

3-Fluoro-N-(2-piperidin-1-yl-ethyl)-4-(3-piperidin-1-yl-propoxy)-benzamide is prepared from 3-Fluoro-4-hydroxy-N-(2-piperidin-1-yl-ethyl)-benzamide (0.1 g, 0.38 mmol) by general procedure A to yield the title compound as an off-white solid (80 mg, 54%). MS (ES+) 392.2

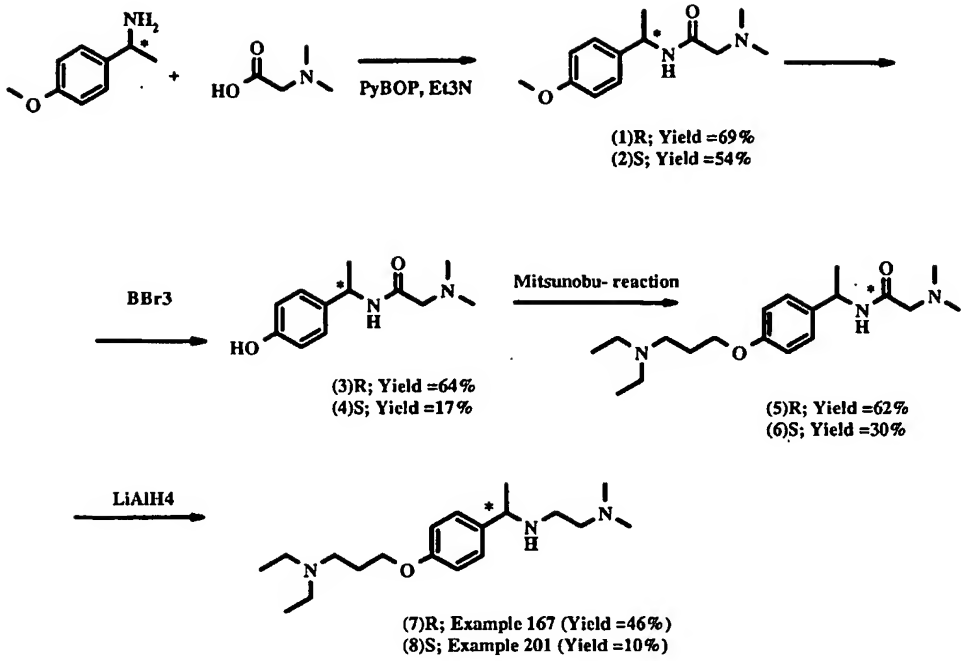


Example 256

(2-Morpholin-4-yl-ethyl)-[4-(3-piperidin-1-yl-propoxy)-benzyl]-amine dihydrochloride:

The dihydrochloride salt was prepared from (2-morpholin-4-yl-ethyl)-[4-(3-piperidin-1-yl-propoxy)-benzyl]-amine (0.307 g) by dissolving in THF (6 mL) and adding a solution

of HCl in Et_2O (1 M, 0.85 mL). Additional Et_2O was added until the mixture was cloudy, and the mixture was allowed to stand at 0 °C overnight. The white solid was collected by filtration to give the dihydrochloride salt. Anal. Calculated for $C_{21}H_{35}N_3O_2 \cdot 2$ HCl: C, 58.06; H, 8.58; N, 9.67; Cl, 16.32. Found: C, 58.0; H, 8.51; N, 9.57; Cl, 16.99.



Synthesis of (1)

1.50g of ®(+)-1-(4-methoxyphenyl) ethylamine (10.0mmol), 2.06g of N, N-Dimethylglycine (20.0mmol) and 2.58g of N, N-Di-isopropylethylamine (20.0mmol) were dissolved in 50ml of CH_2Cl_2 and 6.78g of PyBOP (13.0mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 4h. The reaction mixture was diluted with 20ml of CH_2Cl_2 and washed with brine, 0.1N Hl, brine satNaHCO3 and brine. The separated organic layer was dried over NaSO4 and evaporated. The crude product was applied to short silica-gel column chromatography (CH_2Cl_2 → CH_2Cl_2 : 2M NH3 in MeOH = 20:1) and pure product was recrystalized from Et2O/ CH_2Cl_2. White powder. 1.62g(69%). C/MS : m/z 237(M+1)

Synthesis of (2)

This compound was synthesized according to the method described in the preparation of (1).

Synthesis of (3)

500mg of compound (1) (2.12mmol) was dissolved in 5.0ml of CH_2Cl_2 and cooled to 0 °C. 10.0ml of BBr3 1.0M in CH_2Cl_2 (10mmol) was added slowly and stirred at 0°C for 1h. MeOH was added to quench the reaction and 4.0ml of 5NaOHaq. was added. The mixture was stirred at 0°C for 10min. CH_2Cl_2 layer was separated. The water layer was acidified slowly PH=14→2 and extracted with CH_2Cl_2 for each step. The water layer was concentrated *in vacuo*, filtered off NaCl. The filtrate was made to PH=10 stepwise and extracted with CH_2Cl_2 each step. All of these extractions were combined together, dried over NaSO4 and evaporated to give the product 301mg (64%). LC/MS : m/z 223(M+1)

Synthesis of (4)

This compound was synthesized according to the method described in the preparation of (3).

Synthesis of (5)

52mg of compound (3) (0.23mmol), 57mg of 3-diethylaminopropanol (0.28mmol) and 73mg of Triphenylphosphine (0.28mmol) were dissolved in 2.0ml of dry THF. The air was replaced to N_2 gas. 37mg of Diisopropyl-azodicarboxylate (0.28mmol) in 0.5ml of THF was added to this reaction mixture and stirred at room temparature for overnight. The reaction mixture was concentrated and applied to SCX column, washed by MeOH. The crude product was eluted with 2M NH3 in MeOH. This crude product was applied to silica-gel column chromatography (CH_2Cl_2 : 2M NH3 in MeOH = 20:1) to give the product. 48mg (62%). LC/MS : m/z 336(M+1)

Synthesis of (6)

This compound was synthesized according to the method described in the preparation of (5).

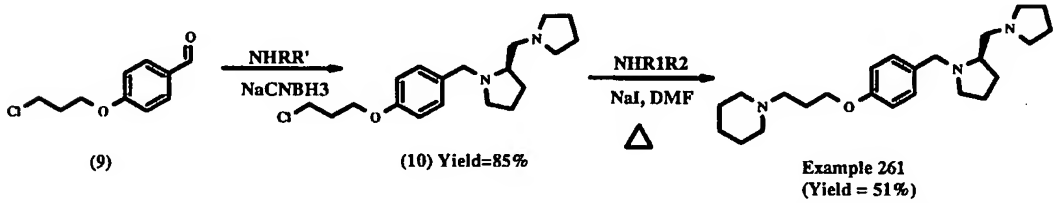
Synthesis of (7)

3.0ml of Litium aluminium hydride 1.0M in THF (3.0mmol) was placed in flask and the air was replaced to N2gas. 43mg of compound (5) (0.13mmol) in 2.0ml of THF was added slowly into the flask and stirred under reflux for 2h. The reaction mixture was

allowed to cool to room temperature and water was added to quench the reaction. The organic layer was decanted. The water layer was extracted with CH_2Cl_2 (3 times) and all organic layers were combined together. This solution was dried over NaSO4 and evaporated. The crude product was applied to silica-gel column chromatography (CH_2Cl_2: 2M NH3 in MeOH = 20:1) to give the product. 19mg (46%). LC/MS : m/z 322(M+1)

Synthesis of (8)

This compound was synthesized according to the method described in the preparation of (7).

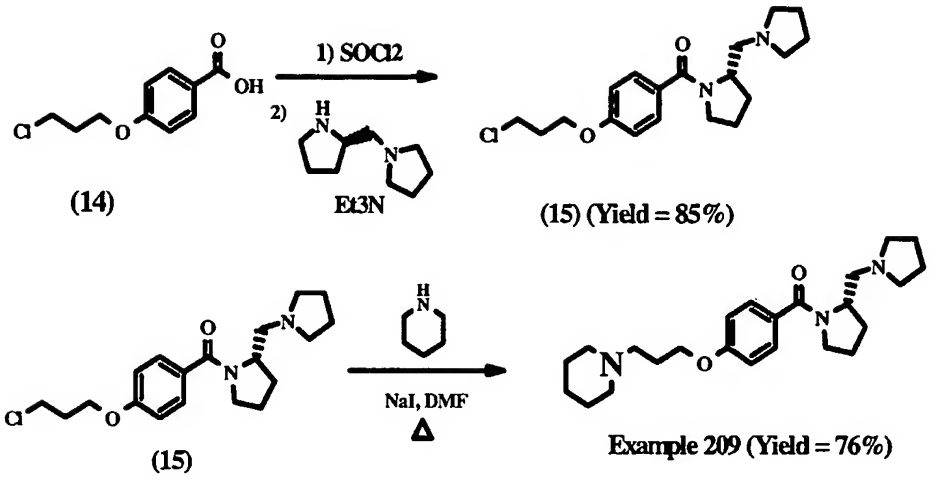


(9) (10) Yield=85% Example 261 (Yield = 51%)

Synthesis of (10) 100mg of compound (9) (0.50mmol) and 116mg of (R)(-)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.75mmol) were dissolved in 5.0ml of 5%AcOH in CH_2Cl_2 and 310mg of MP-cyanoborohydride (mmo/g =2.42, 0.75mmol) was added in the reaction vial. The vial was capped by Teflon cap and shaken at 60°C for overnight. The reaction mixture was filtered and the filtrate was concentrated under N2 gas. The crude product was applied to silica-gel column chromatography (CH_2Cl_2 : 2M NH3 in MeOH = 20:1) to give the product. 143mg (85%). LC/MS : m/z 337(M+1)

Synthesis of Example 261

65 mg of compound (10) (0.19mmol) and 50mg of piperidine (0.58mmol) were put into 4.0ml vial and 2.0ml of THF and 10mg of NaI were added to the vial. The vial was capped by Teflon cap and heated at 100°C for 3days. The reaction mixture was concentrated under N2gas and applied to silica-gel column chromatography (CH_2Cl_2 : 2M NH3 in MeOH = 20:1) to give the product. 38mg (51%). LC/MS : m/z 386(M+1)

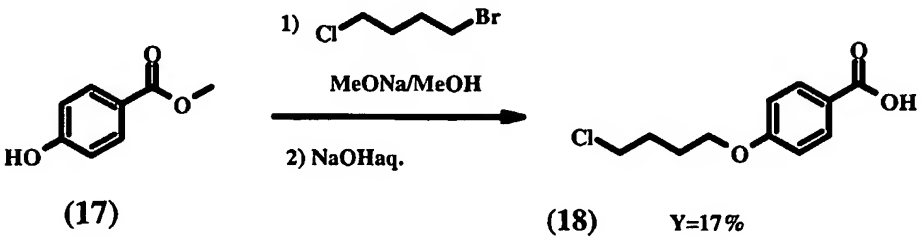


Synthesis of (15)

813mg of compound (14) (98536) (3.8mmol) was dissolved in 5.0ml of thionyl chloride and stirred at 70°C for 1h under N2 gas. The excess acid chloride was removed *in vacuo*. The residue was dissolved in 1.0ml of CH_2Cl_2 to make acid chloride solution. 643mg of (S)(+)-1(2-pyrrolidinylmethyl)pyrrolidine (4.17mmol) and 421mg of triethylamine (4.17mmol) were dissolved in 10ml of CH_2Cl_2 and cooled to 0°C. Acid chloride solution was added to this mixture at 0°C and stirred at room temperature for 2h. The reaction mixture was diluted with CH_2Cl_2 and washed by brine. The crude product was applied to silica-gel column chromatography (CH_2Cl_2 : 2M NH3 in MeOH = 10:1) to give the product. 1.13g (85%) LC/MS : m/z 351(M+1)

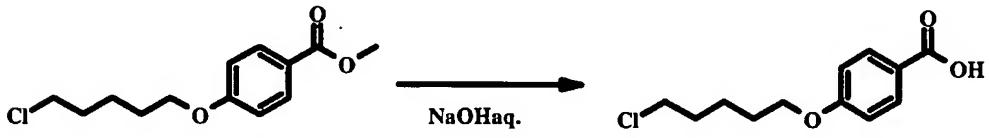
Synthesis of Example 209

This compound was synthesized according to the method described in the preparation of Example 261.



Synthesis of (18)

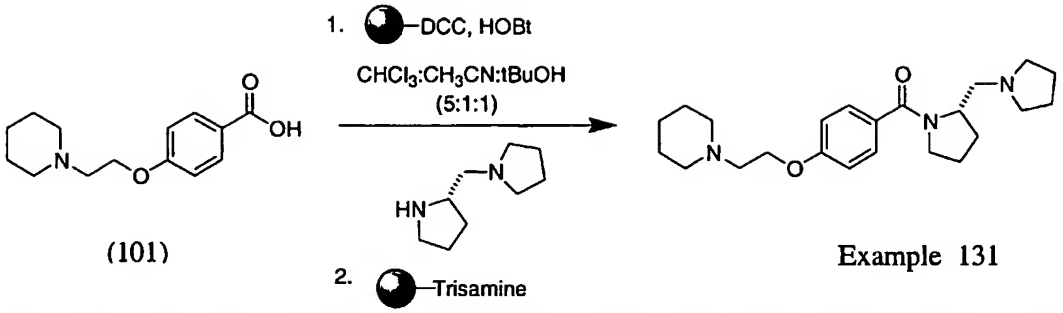
1.17g of Na(51mmol) was dissolved in 200ml of MeOH and 6.48g of methyl p-hydroxy benzoate(17) (42.5mmol) was added followed by 20.52g of 1-bromo 4-chlorobutane (119.6mmol). The reaction mixture was stirred at room temperature for 2h and stirred at 60°C for 1h. Almost of MeOH was removed *in vacuo*. The residue was dissolved in water and acidified by cHCl to PH=1.0 and extracted with CH_2Cl_2. The separated organic layer was dried over NaSO4 and evaporated. The crude product was applied to silica-gel column chromatography (CH_2Cl_2 : 2M NH3 in MeOH = 20:1) to give the product. 1.64g (17%). NMR (DMSO); 7.84(d, 2H, J=5.9Hz), 6.91(d, 2H, J=5.9Hz), 4.02(t, 2H, J=5.8Hz), 3.69(t, 2H, J=6.4Hz), 1.85(m, 4H)



(19) (20) Yield = 77%

Synthesis of (20)

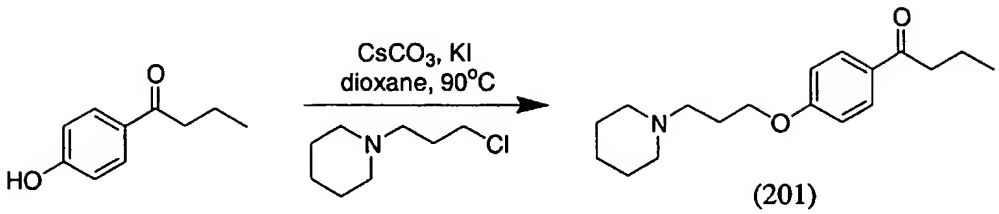
1.14g of compound (19) (4.44mmol) was dissolved in 15ml of MeOH and 10ml of 5N NaOHaq. was added. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was evaporated. The residue was dissolved in water and acidified by cHCl to PH=1.0. This solution was extracted with CH_2Cl_2, dried over NaSO4 and evaporated. The pure product was recrystalized from Hexane/ CH_2Cl_2. 829mg (77%) NMR (DMSO); 8.05(d, 2H, J=8.9Hz), 6.93(d, 2H, J=8.9Hz), 4.05(t, 2H, J=6.3Hz), 3.57(t, 2H, J=6.8Hz), 1.86(m, 4H), 1.65(m, 2H)



(101) Example 131

To a 4 mL vial was placed 101 (28.5 mg, 0.1 mmol), resin-bound DCC (170 mg, 0.16 mmol, 0.94 mmol/g), HOBt (16 mg, 0.12 mmol), amine (13 uL, 0.08 mmol) and a 5:1:1 mixture of $CHCl_3$:CH_3CN:tBuOH. The vial was agitated by means of a lab quake shaker overnight. In the morning, PS-trisamine (134 mg, 0.4 mmol, 3.0 mmol/g) was added and the reaction again allowed to rotate overnight to scavenge excess carboxylic acid and HOBt. Filtration, washing with DCM/MeOH and concentration afforded a orange foam. Filtration through a short pipet column provided 25 mg (83%) of an yellow solid, 629304. Mass spec hit M+1, 386; LCMS >95% @ 230 nm and ELSD. A substantially analogous procedure was employed for the array synthesis of Examples:

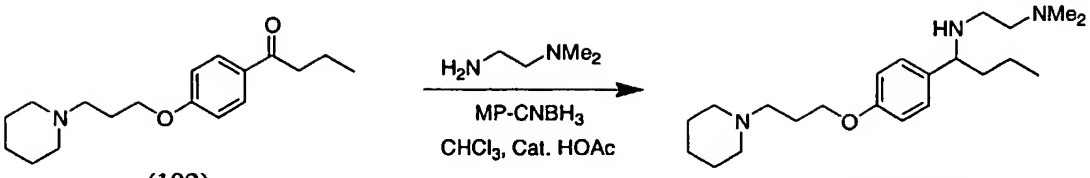
Example #	Observed Mass
41	361
42	361
44	389
43	401
130	386
131	386
132	401
133	372
144	400
150	360
151	340
152	346
153	360
154	360
155	386
173	358



(201)

1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-butan-1-one

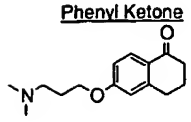
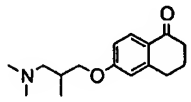
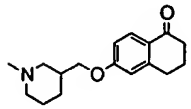
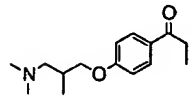
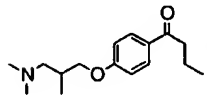
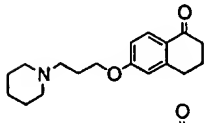
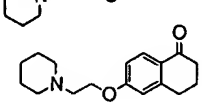
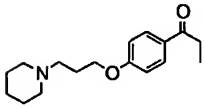
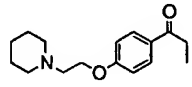
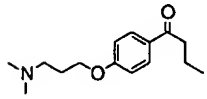
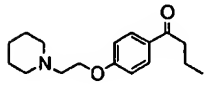
To a 20 mL vial was placed keto-phenol (500 mg, 3 mmol), $CsCO_3$ (1.98 g, 6 mmol), KI (454 mg, 3 mmol) and chloropropylpiperdine (64 mg, 3.3 mmol). Dioxane added and the reaction was heated to 90 degrees overnight on a J-KEM heater/shaker block. The reaction was then quenched with water, extracted into DCM and dried over Na2SO4. The material was purified by Biotage utilizing 4:1 EtOAc:MeOH to afford (201) as a orange oil (880 mg, 99%). Mass spec hit M+1, 290; LCMS >95% @ 230 nm and ELSD.

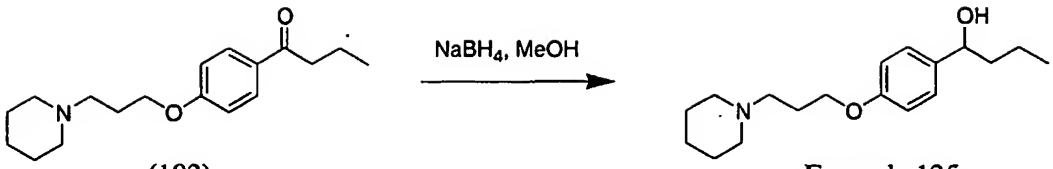


(102) Example 94

Example 94, and 192.

To a 20 mL vial was placed (102) (300 mg, 1 mmol), diamine (120 mg, 1.14 mmol), MP-$CNBH_3$ (2.4 g, 6.22 mmol) and a 9:1 $CHCl_3$:HOAc solution. The reaction was heated to 50 degrees overnight on a J-KEM heater/shaker block. The reaction was filtered, washed with DCM/MeOH. The material was then subjected to preparative HPLC purification to afford 29 mg (3%) of analytically pure example 94. as a white solid. Mass spec hit M+1, 362; LCMS >98% @ 230 nm and ELSD. Example 192 can be made by a substantially analogous procedure, Observed mass 360. The following examples are made by a substantially analogous procedure:

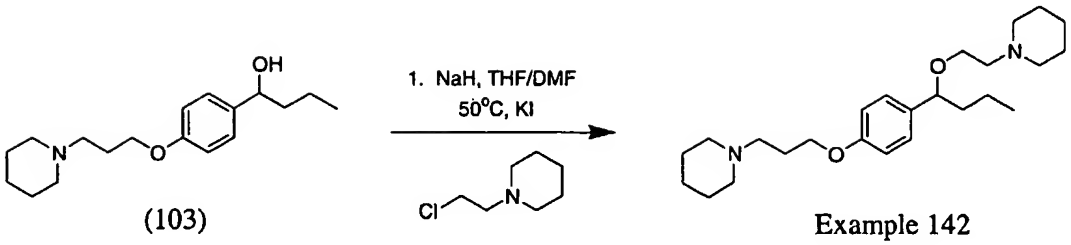
Phenyl Ketone	Product Name	Example	(M+1)
	*N*-[6-(3-Dimethylamino-propoxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-*N*,*N*-dimethyl-ethane-1,2-diamine	84	320
	*N*-[6-(3-Dimethylamino-2-methyl-propoxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-*N*,*N*-dimethyl-ethane-1,2-diamine	85	246 M-87
	*N*,*N*-Dimethyl-*N*-[6-(1-methyl-piperidin-3-ylmethoxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-ethane-1,2-diamine	86	346
	*N*-{1-[4-(3-Dimethylamino-2-methyl-propoxy)-phenyl]-propyl}-*N*,*N*-dimethyl-ethane-1,2-diamine	87	322
	*N*-{1-[4-(3-Dimethylamino-2-methyl-propoxy)-phenyl]-butyl}-*N*,*N*-dimethyl-ethane-1,2-diamine	88	336
	*N*,*N*-Dimethyl-*N*-[6-(3-piperidin-1-yl-propoxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-ethane-1,2-diamine	89	272 M-87
	*N*,*N*-Dimethyl-*N*-[6-(2-piperidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-ethane-1,2-diamine	90	258 M-87
	*N*,*N*-Dimethyl-*N*-{1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-propyl}-ethane-1,2-diamine	91	348
	*N*,*N*-Dimethyl-*N*-{1-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-butyl}-ethane-1,2-diamine	92	334
	*N*-{1-[4-(3-Dimethylamino-propoxy)-phenyl]-butyl}-*N*,*N*-dimethyl-ethane-1,2-diamine	93	322
	*N*,*N*-Dimethyl-*N*-{1-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-butyl}-ethane-1,2-diamine	95	348



(102) Example 135

Examples 135, 14, 126 6

To a 10 mL round-bottom flask was added (102) (280 mg, 0.96 mmol) and dry MeOH (5 mL). Then, $NaBH_4$ (74 mg, 1.93 mmol) was added at room temperature. After 1 hour, the reaction was then quenched with water, extracted into DCM and dried over Na_2SO_4. The material was purified by Biotage utilizing 4:1 EtOAc:MeOH to provide 270 mg (98%) of a white solid. Mass spec hit M+1, 292; LCMS >98% @ 230 nm and ELSD. Examples 14 and 126 are made by a substantially analogous procedure. Observed mass: Example 14 = 321, Example 126 = 375.

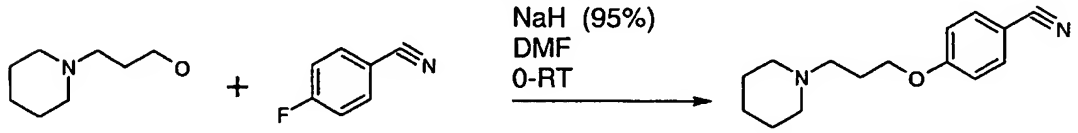


(103) Example 142

Example 142

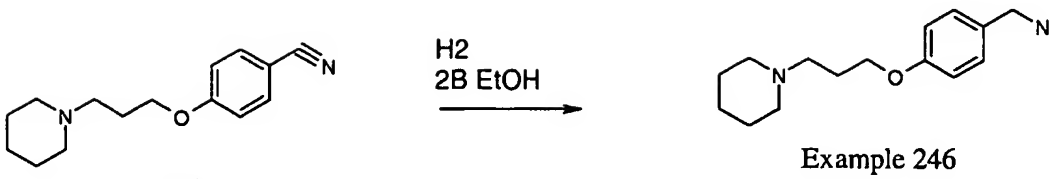
To a round-bottom flask, equipped with stir bar and septum, was placed (103) (300 mg, 1.03 mmol), KI (230 mg, 1.54 mmol) and NaH (78 mg, 95%dry, 3.09 mmol). Then, dry DMF (20 mL, 0.5 M) was added via syringe followed by chloroethylpiperidine (285 mg, 1.54 mmol). The reaction was allowed to stir at 50 degrees overnight. In the morning, the reaction was quenched with water, extracted into EtOAc (3 x 20 mL) and dried over brine. Column chromatography in 9:1 DCM:MeOH afforded 631934 an yellow oil (300 mg, 79%). Mass sec hit M+1, 404; LCMS >95% @ 230 nm and ELSD.

Example 246



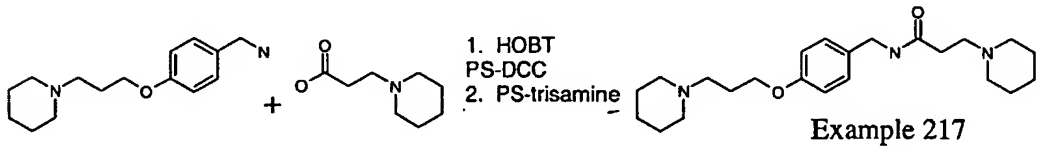
(104)

3-Piperidinylpropanol(3.56g, 25 mmoles) in 4 ml DMF was added to a slurry of sodium hydride in 10 ml DMF at 0 C., and the reaction was stirred at 0 C.for 0.5 hr. The 4-fluorobenzonitrile in 6 ml was added at 0 C. The reaction was stirred at 0 C for 1 hr. and at RT overnight. Water and ether were carefully added. Separated the ether layer and extracted with water five times. The ether extract was dried over sodium sulfate, filtered and evaporated to give 6.0g(0.0246 mmoles, 98.4% yield). LCMS 1.61 min @254.0 nm 95.2%; @230.0 nm 89.5%; ELSD 1.71 min 100%; MS 1.59 min M + 1 = 245 good for product (104).



(104) Example 246

The nitrile(6.0g, 0.0246 mmoles) in 250 ml 2B EtOH with 2.5 g RaNi was hydrogenated at 80 C. for 8 hrs. Filtration and evaporation yielded 5.4 g oil(88.4 yield).



Example 217

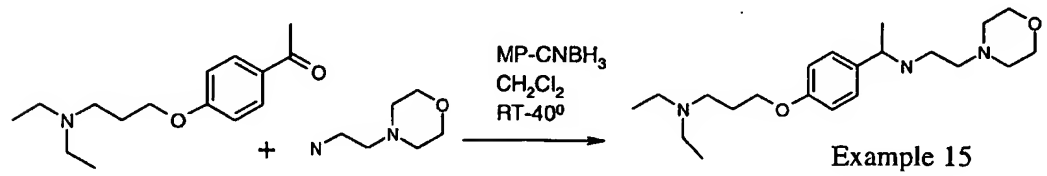
Example 217

The 1-hydroxybenzotriazole hydrate(13.5 mg, 0.1 mmole),1-piperidinepropionic acid(18.1 mg, 0.115 mmole), amine(248 mg, 0.1 mmole), polystyrene-carbodiimide(125 mg, 0.15 mmoles) and 2.5 ml chloroform, acetonitrile, t-butanol(5:1:1) in a 4 ml vial were rotated for four days. Polystyrene-trisamine(93.7 mg, 0.4 mmoles) was added and the reaction was rotated overnight. Filtered reaction through filter cartridge and evaporated to give 37.5 mg, 0.0967 mmole, 96.7% yield. LCMS ELSD 1.42 min 100%, MS 1.21 min M + 1 = 388 good for product.

Example	Observed Mass
116	348
117	376
118	350
119	384
120	391
121	322
122	398
123	393
124	388
125	477

Example 15

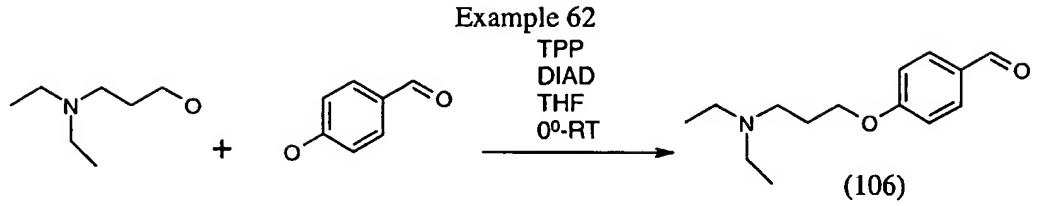
The solution of diisopropylazodicarboxylate(3.93 ml, 20 mmoles) in 20 ml anhydrous THF was added dropwise with stirring to the cold solution of 4-hydroxyacetophenone(2.18 g, 16 mmoles), 3-diethylaminopropanol(2.23 ml, 15 mmoles) and triphenylphosphine(4.98 g, 19 mmoles) in 50 ml anhydrous THF over 45 minutes. The reaction was stirred in an ice bath for one hour and at room temperature for 18 hours. The solvent was evaporated and ether was added. This solution was extracted with dilute HCl(1.0 N) four times. These combined acidic extracts were extracted with ether, basified with a NaOH solution and extracted with ether three times. These combined ethereal extracts were dried over sodium sulfate, filtered and evaporated to give 3.41 g oil. LCMS 1.53 min @254.0 nm 97.4%; ELSD 1.59 min 91.1%; MS 1.58 min M+1=250 good for product (105).



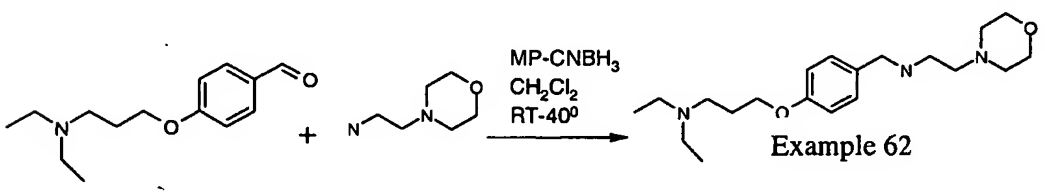
Example 15

In a 7 ml vial with cap, 4-(3-diethylaminopropyloxy)acetophenone(0.47 g, 0.19 mmoles), N-(2-aminoethyl)morpholine(0.039 ml, 0.3 mmoles) and macroporus cyanoborohydride(169 mg, 0.4 mmoles) in 2 ml dichloromethane with 0.2 ml glacial acetic were heated on shaker at 55^0 for 18 hours. Purified with a 3 ml extrelut cartridge hydrated with 3 ml water. The reaction solution was added and the cartridge was rinsed with dichloromethane(5 ml). The product was eluted with 10% triethylamine/dichloromethane. LCMS 1.14 min @254.0 nm 95.6%; @230.0 nm 95.3%; 1.20 min ELSD 95.3%; MS 1.14 min M+1=364 good for product.

Example	Observed Mass
15	364
16	348
17	308
18	362
19	336
20	377
21	391
1	336
22	381
231	363
24	362
25	359
26	336
27	376

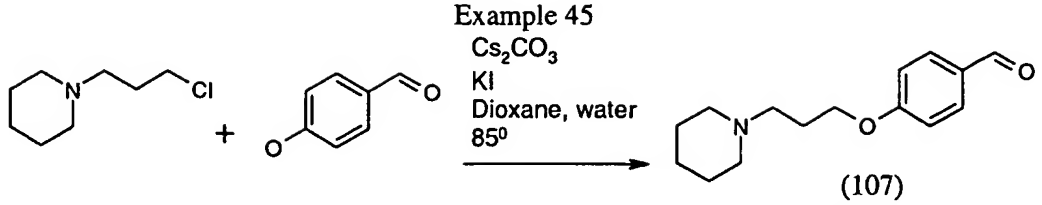


The solution of diisopropylazodicarboxylate (3.93 ml, 20 mmoles) in 20 ml anhydrous THF was added dropwise with stirring to the cold solution of 4-hydroxybenzaldehyde(1.95 g, 16 mmoles), 3-diethylaminopropanol(2.23 ml, 15 mmoles) and triphenylphosphine(4.98 g, 19 mmoles) in 50 ml anhydrous THF over 45 minutes. The reaction was stirred in an ice bath for one hour and at room temperature for 18 hours. The solvent was evaporated and ether was added. This solution was extracted with dilute HCl(1.0 N) four times. These combined acidic extracts were extracted with ether, basified with a NaOH solution and extracted with ether three times. These combined ethereal extracts were dried over sodium sulfate, filtered and evaporated to give 3.71 g oil. LCMS 1.47 min @254.0 nm 97.0%; ELSD 1.53 min 95.4%; MS 1.48 min M+1=236 good for product.



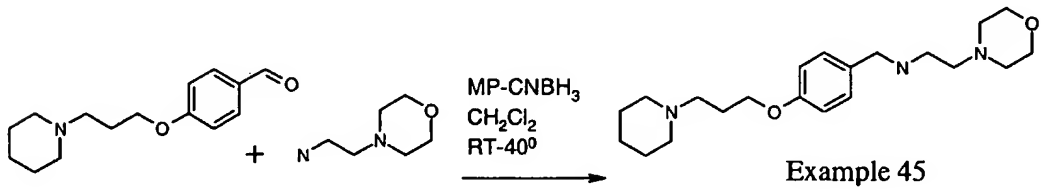
In a 7 ml vial with cap, 4-(3-diethylaminopropyloxy)benzaldehyde(0.59 g, 0.25 mmoles), N-(2-aminoethyl)morpholine(0.049 ml, 0.375 mmoles) and macroporus cyanoborohydride(210 mg, 0.5 mmoles) in 3 ml dichloromethane with 0.3 ml glacial acetic were heated on shaker at 40^0 briefly. Purified with 3 ml extrelut cartridge hydrated with 3 ml water. The reaction solution was added and the cartridge was rinsed with dicloromethane(5 ml). The product was eluted with 10% triethylamine/dichloromethane. LCMS 1.14 min ELSD 95.3%; MS 1.09 min M+1=350 good for product Example 62.

Example	Observed Mass
629	350
63	334
47	294
48	348
49	348
50	322
51	363
52	377
61	322
53	349
54	348
70	345
71	322
72	362
73	364
59	376
74	348
104	320
113	420
114	410
107	334
103	334



(107)

4-Hydroxybenzaldehyde(2.44g, 20 mmoles), N-(3-Chloropropyl)piperidine hydrochloride, cesium carbonate(19.7 g, 60 mmoles) and potassium iodide in 14 ml dioxane with 0.7 ml water were stirred at 85^0 for 8 hours and at room temperature for 16 hours. Evaporated the decanted supernatant, added water to both (evaporated supernatant and solid) and extracted three times with ether. These combined ethereal extracts were washed three times with water, dried over sodium sulfate, filtered and evaporated to give 7.8 g oil. LCMS 1.48 min @254.0 nm 99.4%; @230.0 nm 89.6%; 1.51 min ELSD 99.4%; MS 1.49 min M+1=248 good for product. 300 mHz NMR(CDCl3) good for structure (107).

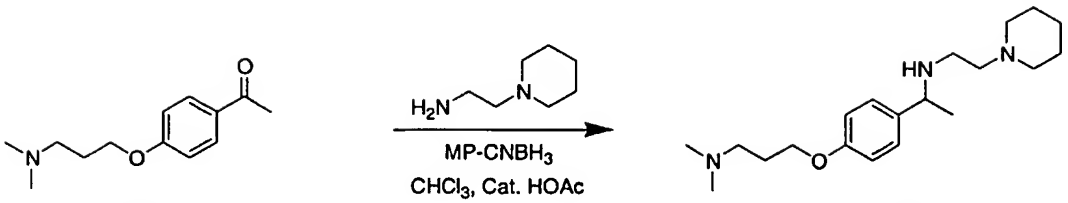


Example 45

In a 7 ml vial with cap, 4-[(3-N-piperidinyl)propyloxy]benzaldehyde(0.062 g, 0.25 mmoles), N-(2-aminoethyl)morpholine(0.049 ml, 0.375 mmoles) and macroporus cyanoborohydride(210 mg, 0.5 mmoles) in 3 ml dichloromethane with 0.3 ml glacial acetic were heated on shaker at 40^0. The reaction was shaken at room temperature for 16 hours and at 40^0 for one hour. Purified with 3 ml extrelut cartridge hydrated with 3 ml water. The reaction solution was added and the cartridge was rinsed with dicloromethane(5 ml). The product was eluted with 10% triethylamine/dichloromethane. LCMS 1.13 min @230.0 nm 97.3%; 1.19 min ELSD 98.5%; MS 1.13 min M+1=362 good for product Example 45.

Example	Observed Mass
45	362
46	346
64	306
65	360
66	360
67	334
68	361
69	360
55	357
56	334
57	374
58	376
75	388
60	360
102	346
105	332
112	432
115	410
106	346
108	375
109	389
110	334

Example 100

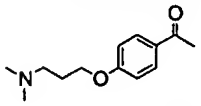
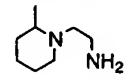
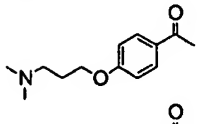
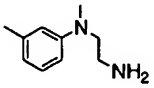
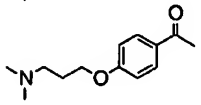
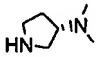
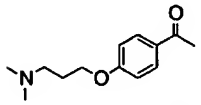
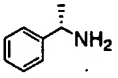
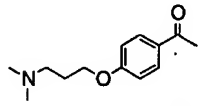
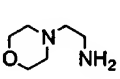
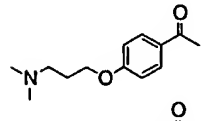
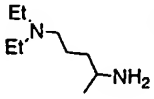
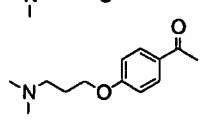
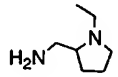
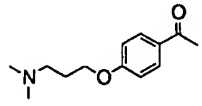
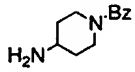
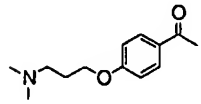
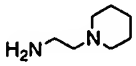
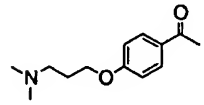
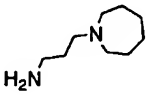
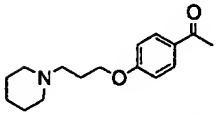
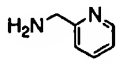
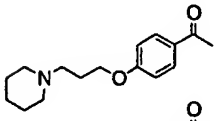
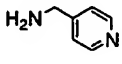
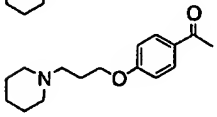
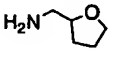


(108) Example 100

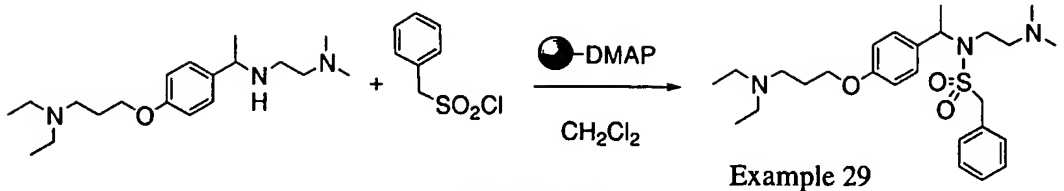
Dimethyl-(3-{4-[1-(2-piperidin-1-yl-ethylamino)-ethyl]-phenoxy}-propyl)-amine

To a 20 mL vial was placed (108) (42 mg, 0.19 mmol), amine (37 mg, 0.29 mmol), MP-$CNBH_3$ (190 mg, 0.45 mmol, 2.37 mmol/g) and a 9:1 $CHCl_3$:HOAc solution. The reaction was heated to 50 degrees overnight on a J-KEM heater/shaker block. The reaction was filtered, washed with DCM/MeOH. The material was then subjected to preparative HPLC purification to afford 5.8 mg (9%) example 100. As a clear oil. Mass spec hit M+1, 334; LCMS >89% @ 214 nm.

In a procedure substantially similar to that for synthesis if Example 100, the following examples are made:

Amino Ketone	Amine	Product Name	Example	MS	
		Dimethyl-[3-(4-{1-[3-(2-methyl-piperidin-1-yl)-propylamino]-ethyl}-phenoxy)-propyl]-amine	613123 12	362	
		*N*-{1-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-*N*-ethyl-*N*-*m*-tolyl-ethane-1,2-diamine	613021 11	384	
		(1-{1-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-pyrrolidin-3-yl)-dimethyl-amine	613011	320	
		Dimethyl-(3-{4-[1-(1-phenyl-ethyl amino)-ethyl]-phenoxy}-propyl)-amine	10 96	327	
		Dimethyl-(3-{4-[1-(2-morpholin-4-yl-ethylamino)-ethyl]-phenoxy}-propyl)-amine	623901	335	
		N^4-{1-[4-(3-Dimethylamino-propoxy) phenyl]-ethyl}-N^1,N^1-diethyl-pentane-1,4-diamine	97 98	363	
		[3-(4-{1-[(1-Ethyl-pyrrolidin-2-yl methyl)-amino]-ethyl}-phenoxy)-propyl]-dimethyl-amine	623903	333	
		(1-Benzyl-piperidin-4-yl)-{1-[4-(3-dimethylamino-propoxy)-phenyl]-ethyl}-amine	99	395	
		Dimethyl-(3-{4-[1-(2-piperidin-1-yl-ethylamino)-ethyl]-phenoxy}-propyl)-amine	100	333	
		(3-{4-[1-(3-Azepan-1-yl-propyl amino)-ethyl]-phenoxy}-propyl)-dimethyl-amine	101	361	
		{1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-ethyl}-pyridin-2-ylmethyl-amine	36	354	
		{1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-ethyl}-pyridin-4-ylmethyl-amine	37	354	
		{1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-ethyl}-(tetrahydro-furan-2-ylmethyl)-amine	40	347	PG6-A40-154-21

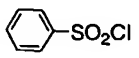
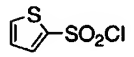
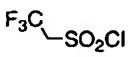
5



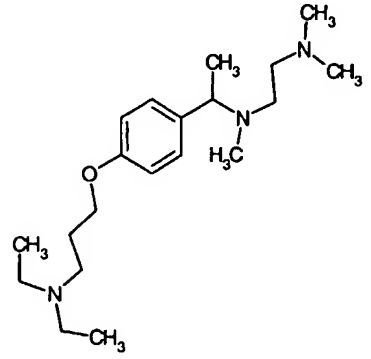
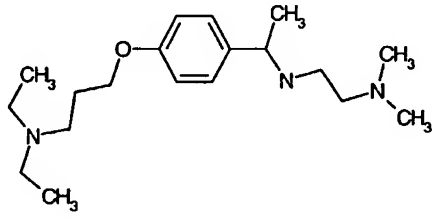
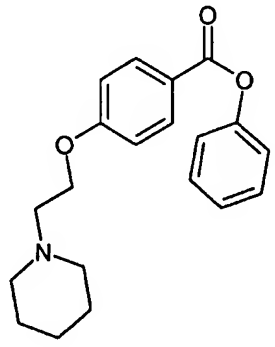
Example 29

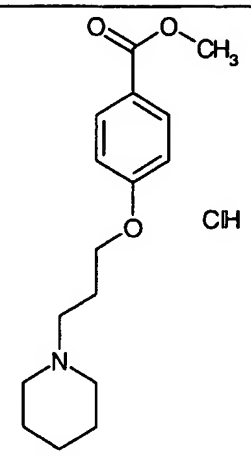
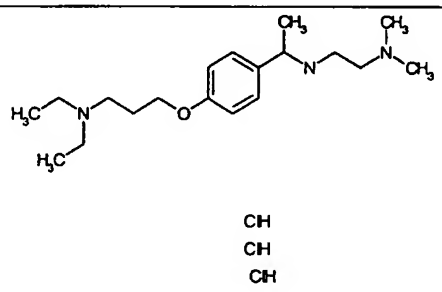
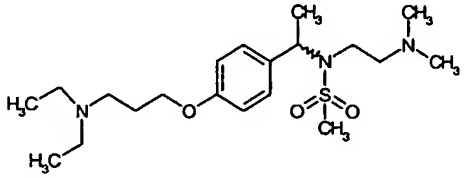
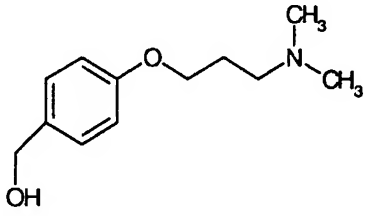
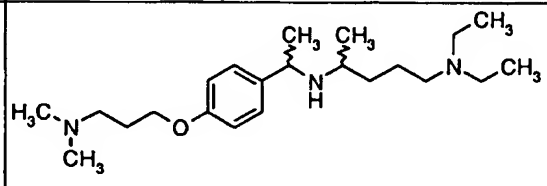
Example 29

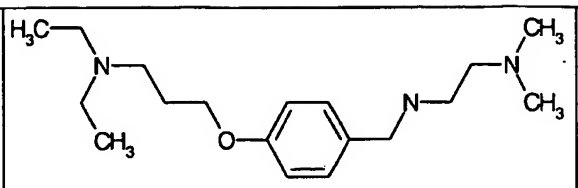
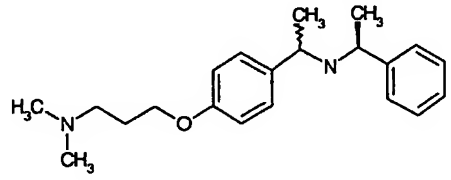
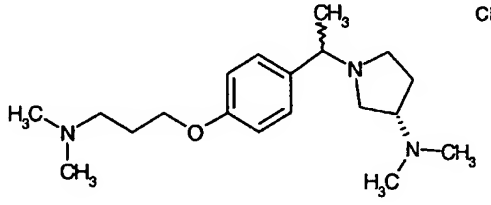
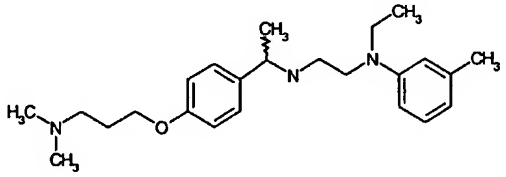
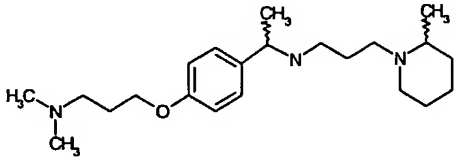
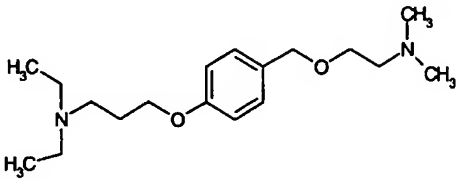
N-{1-[4-(3-Diethylamino-propoxy)-phenyl]-ethyl}-*N*-(2-dimethylamino-ethyl)-*C*-phenyl-methanesulfonamide. To a 4 ml vial was placed N-{1-[4-(3-Diethylamino-propoxy)-phenyl]-ethyl}-N',N'-dimethyl-ethane-1,2-diamine (22 mg, 0.07 mmol), phenyl-methanesulfonyl chloride (27 mg, 0.14 mmol), PS-DMAP (93 mg, 1.48 mmol/g), and CH_2Cl_2 (1.5 ml). The vial was agitated by means of a lab quake shaker for 4 h. To the solution was added PS-Trisamine (100 mg, 3.3 mmol, 3.0 mmol/g) and the reaction was allowed to agitate overnight to scavenge excess methansulfonyl chloride. Filtration, washing with CH_2Cl_2 and concentrating afforded *N*-{1-[4-(3-Diethylamino-propoxy)-phenyl]-ethyl}-*N*-(2-dimethylamino-ethyl)-*C*-phenyl-methanesulfonamide. Mass spec hit M+1, 476: LCMS >93% @ 230 nm and ELSD.

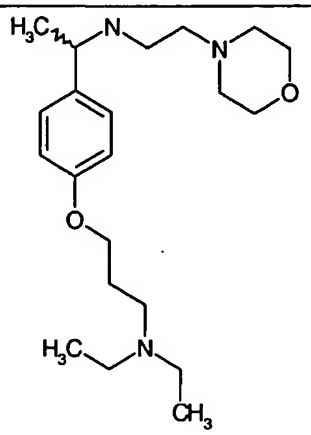
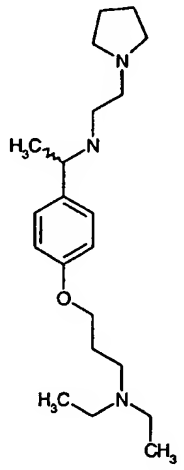
Sulfonyl Chloride	Product Name	Example	MS (M+1)
	*N*-{1-[4-(3-Diethylamino-propoxy)-phenyl]-ethyl}-*N*-(2-dimethylamino-ethyl)-benzenesulfonamide	30	462
	Thiophene-2-sulfonic acid {1-[4-(3-diethylamino-propoxy)-phenyl]-ethyl}-(2-dimethylamino-ethyl)-amide	33	468
	2,2,2-Trifluoro-ethanesulfonic acid {1-[4-(3-diethylamino-propoxy)-phenyl]-ethyl}-(2-dimethylamino-ethyl)-amide	31	468

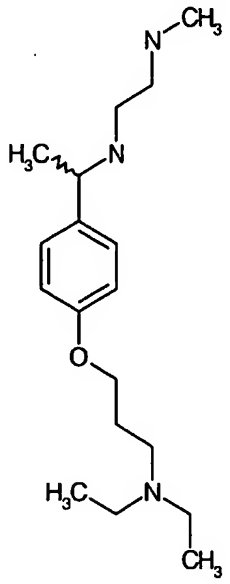
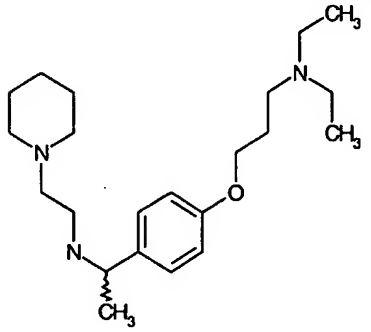
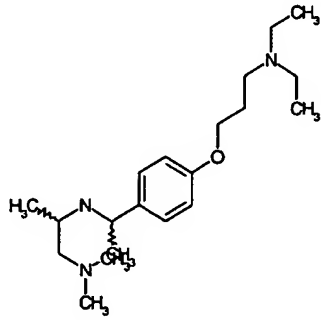
Utilizing the procedures provided herein, in addition to methods known in the art, compounds of Formula I and Formula II were prepared. Structural figures for representative examples of Formula I and Formula II are shown the following pages.

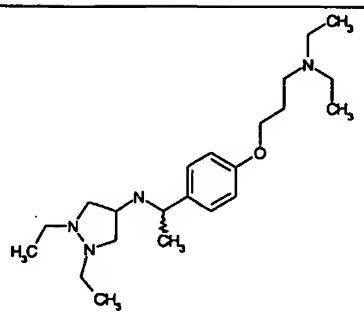
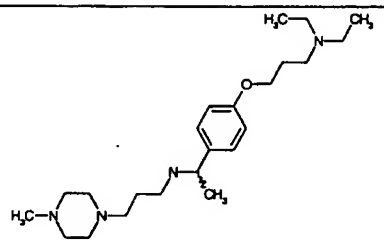
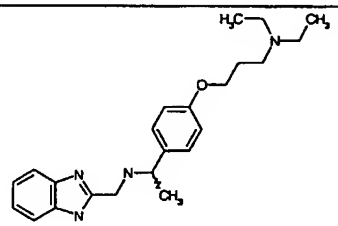
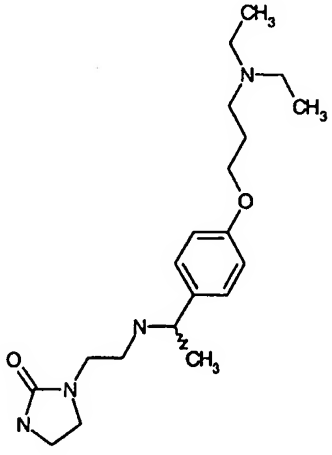
	Example Number	Structure	Observed Mass	
	1		336	
	2		321.2	
	3			

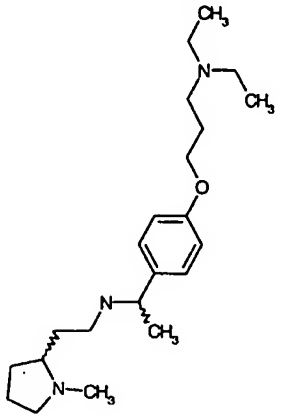
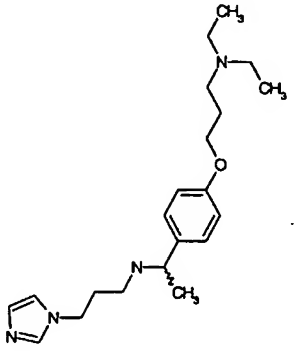
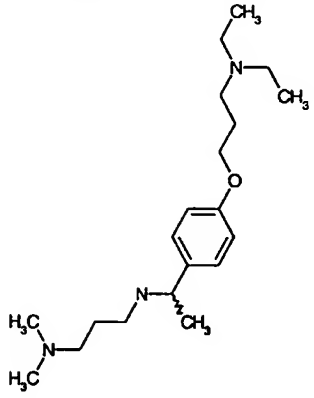
	4			
	5		321.2	
	6		400.2	
	7		210.3	
	8			

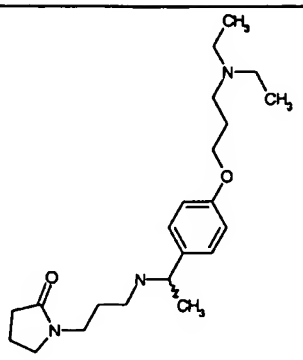
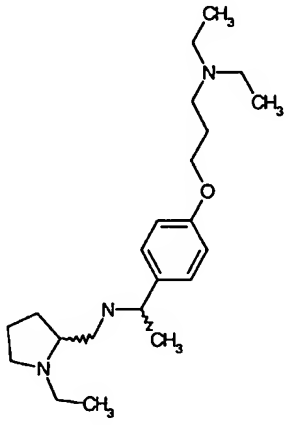
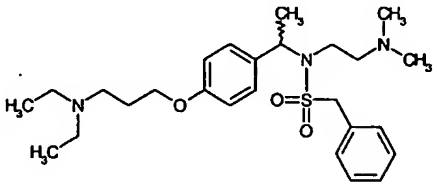
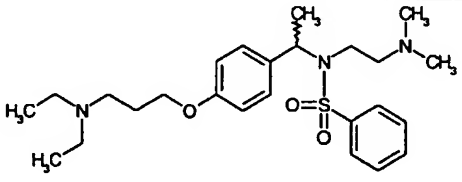
	9		308	
	10		327	
	11		320	
	12		384	
	13		362	
	14		321	

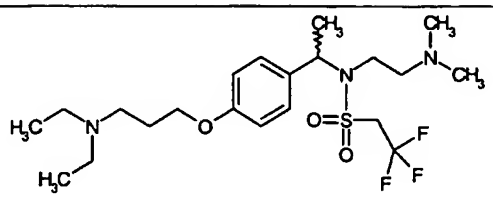
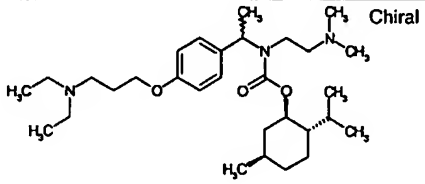
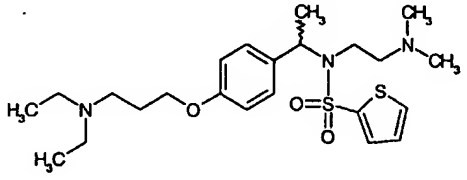
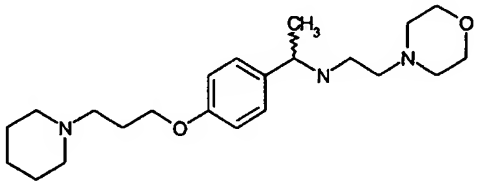
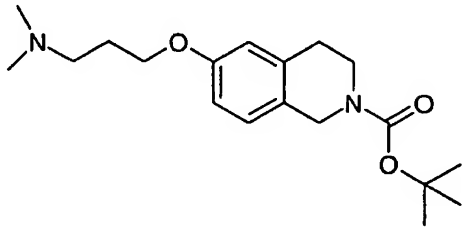
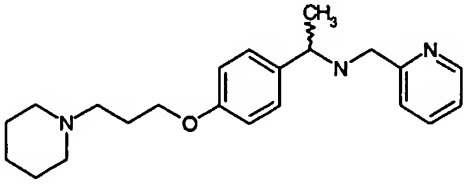
	15		363	
	16		348	

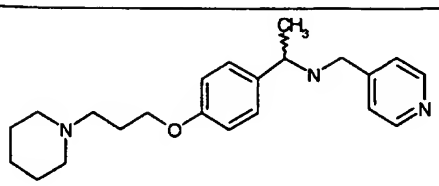
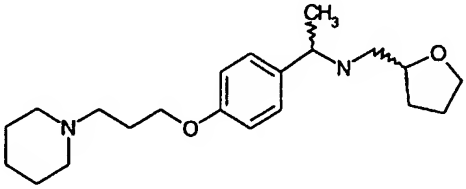
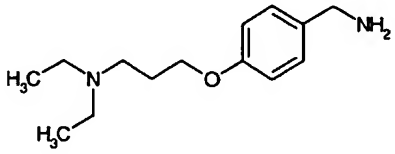
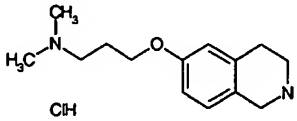
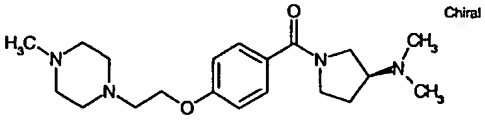
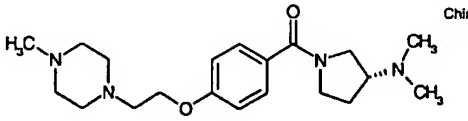
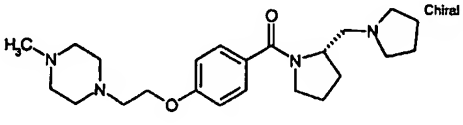
	17		308	
	18		362	
	19		336	

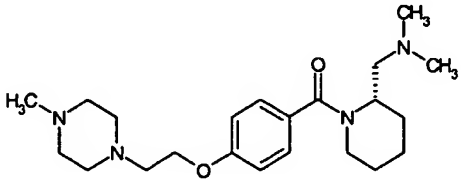
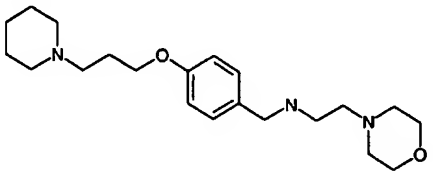
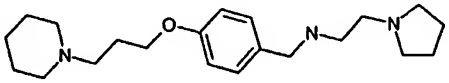
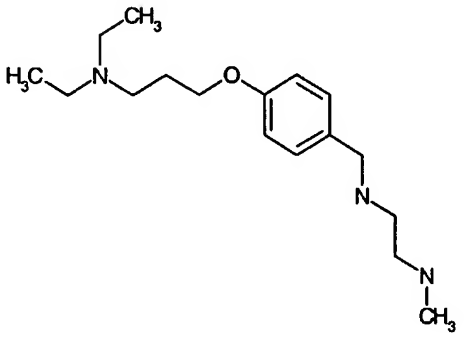
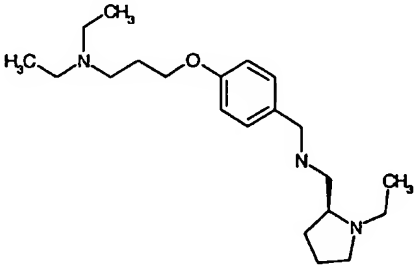
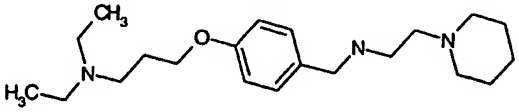
	20		377	
	21		391	
	22		381	
	23		376	

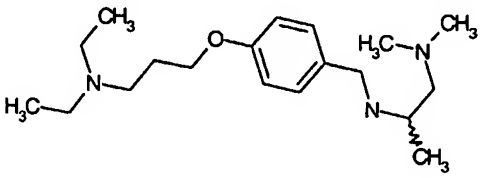
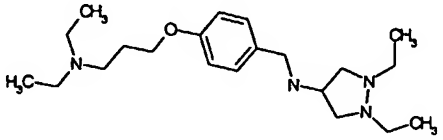
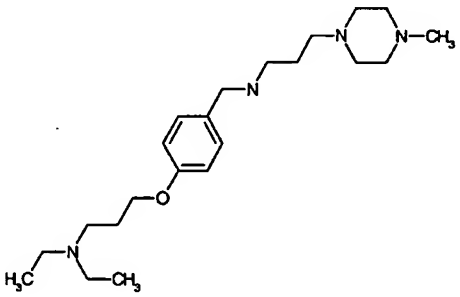
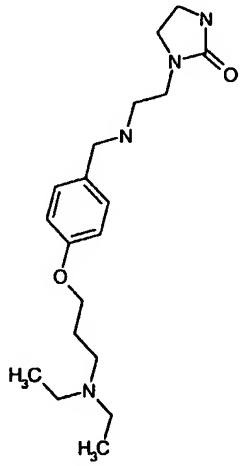
	24		362	
	25		359	
	26		336	

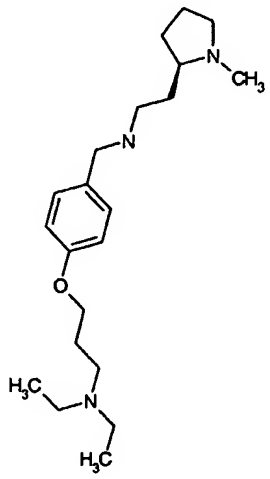
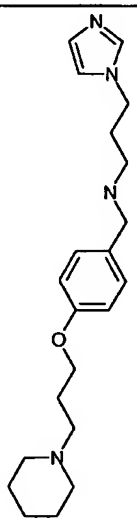
	27		376	
	28		362	
	29		476	
	30		462	

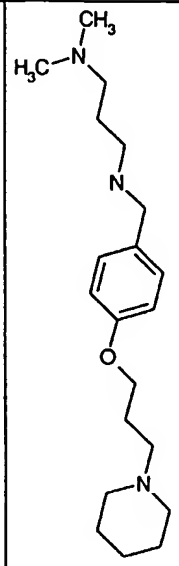
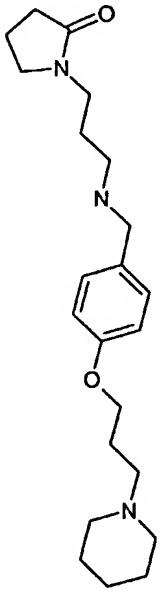
	31		468	
	32	 Chiral		
	33		468	
	34			
	35		335	
	36		354	

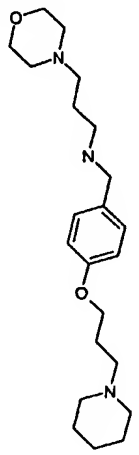
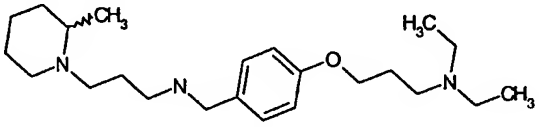
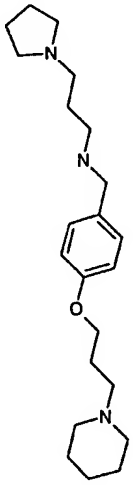
	37		354	
	38			
	39			
	40	 ClH ClH	235	
	41	 Chiral	361	
	42	 Chiral	361	
	43	 Chiral	401	

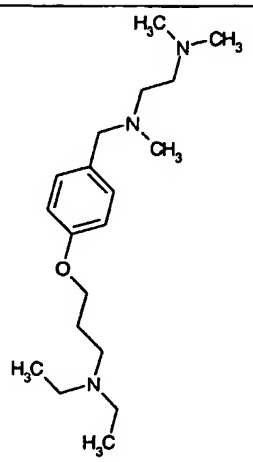
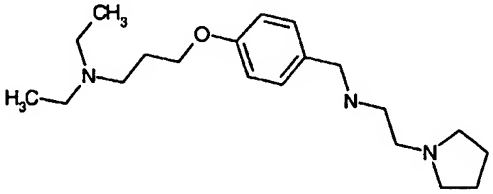
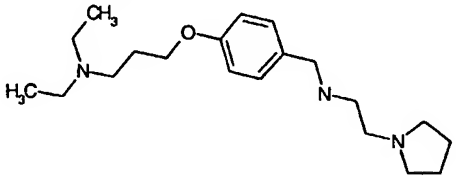
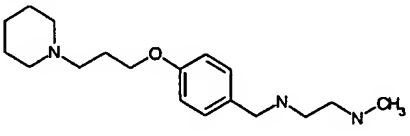
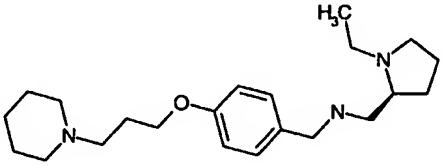
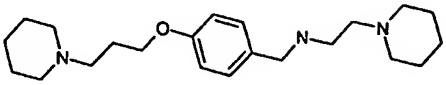
	44		389	
	45		362	
	46		346	
	47		294	
	48		348	
	49		348	

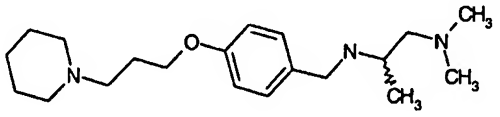
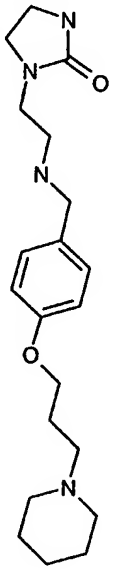
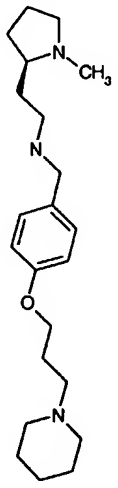
	50		322	
	51		363	
	52		377	
	53		349	

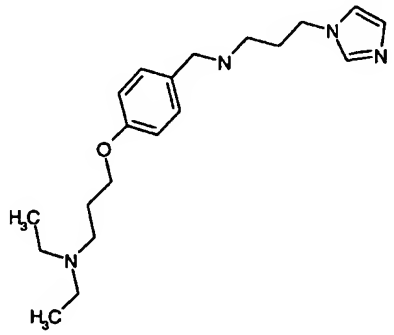
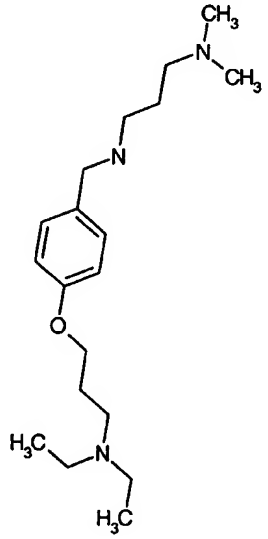
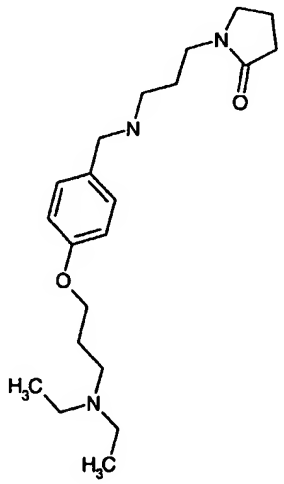
	54		348	
	55		357	

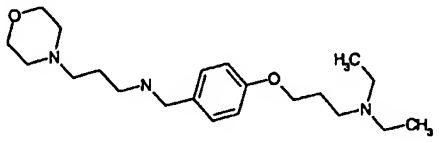
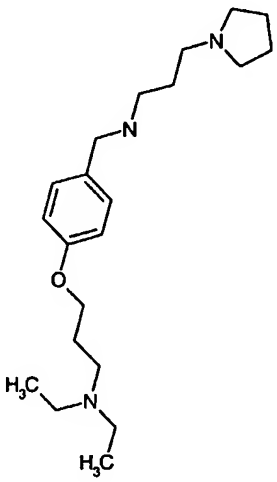
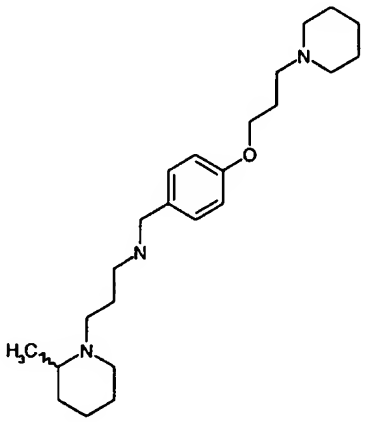
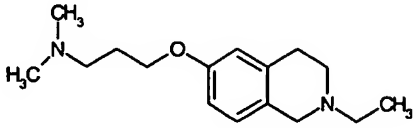
	56		334	
	57		374	

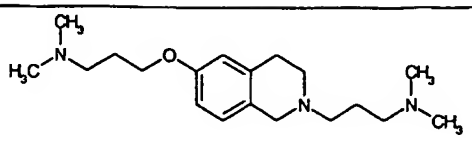
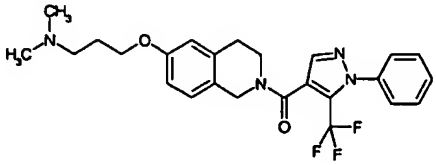
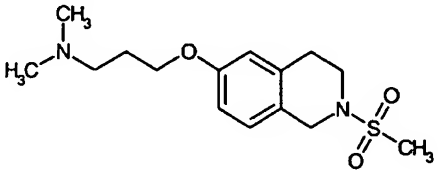
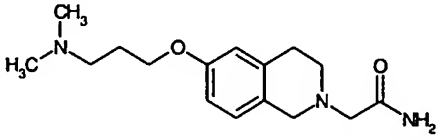
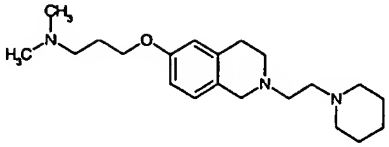
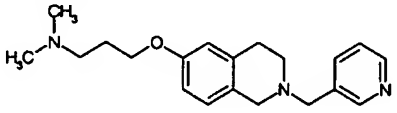
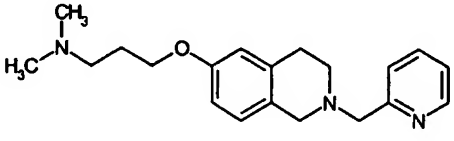
	58		376	
	59		376	
	60		360	

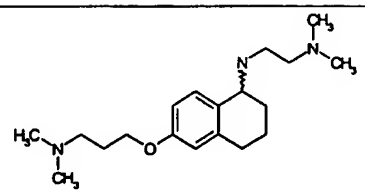
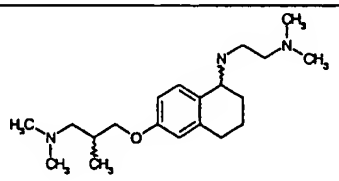
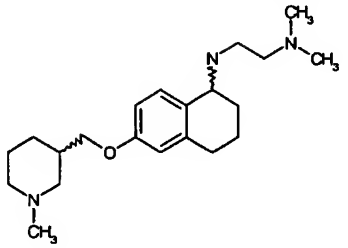
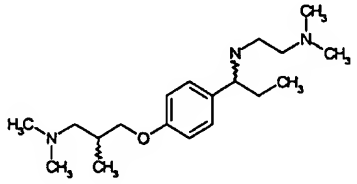
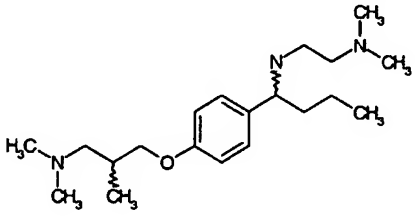
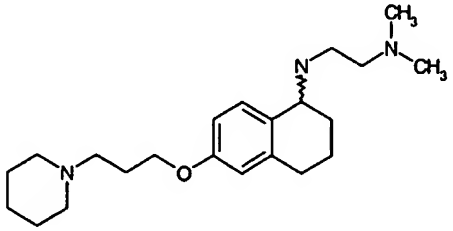
	61		322	
	62		350	
	63		334	
	64		306	
	65		360	
	66		360	

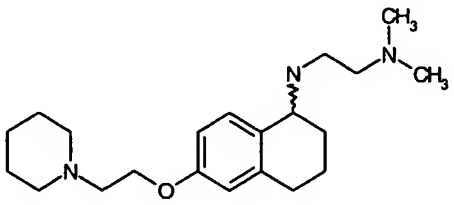
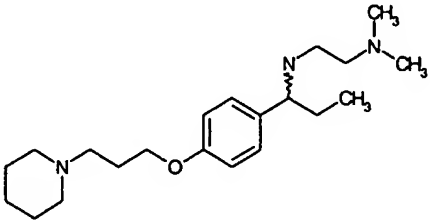
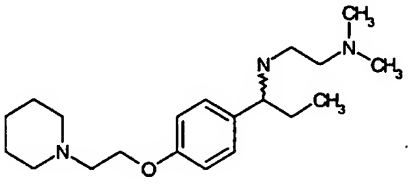
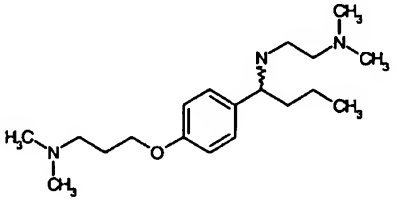
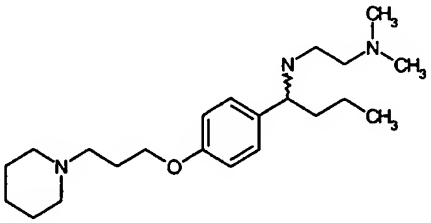
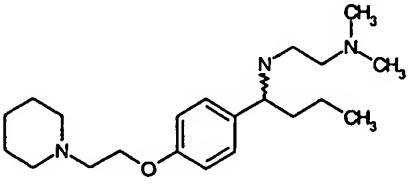
	67		334	
	68		361	
	69		360	

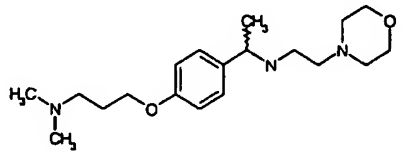
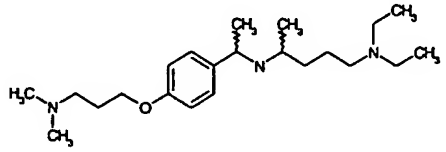
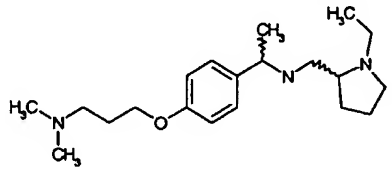
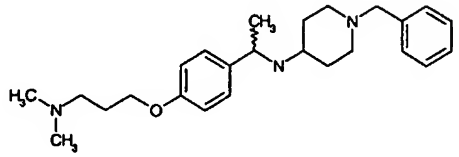
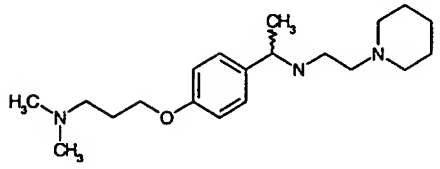
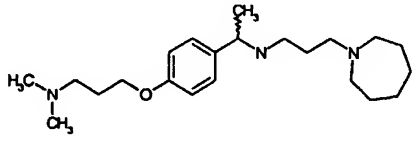
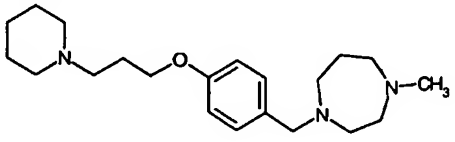
	70		345	
	71		322	
	72		362	

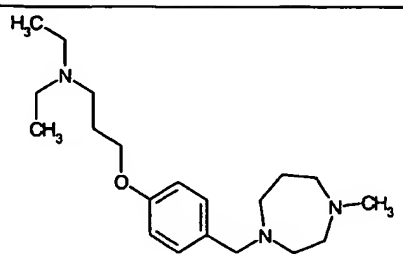
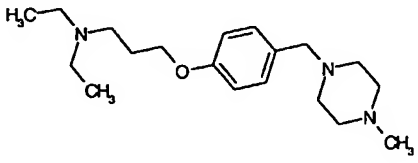
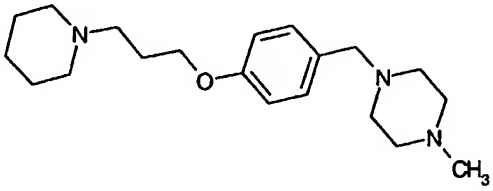
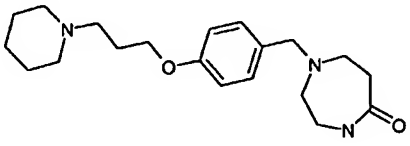
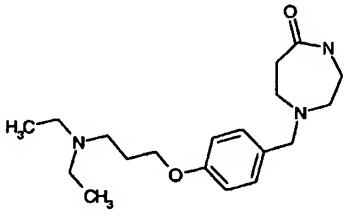
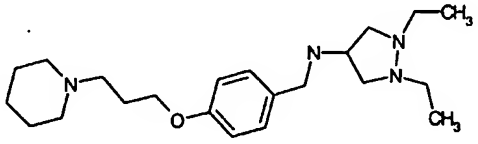
	73		364	
	74		348	
	75		388	
	76		263	

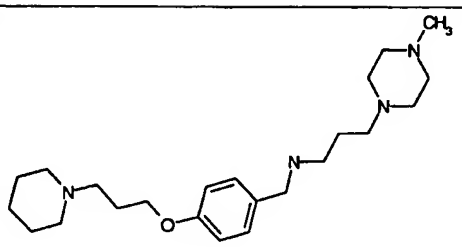
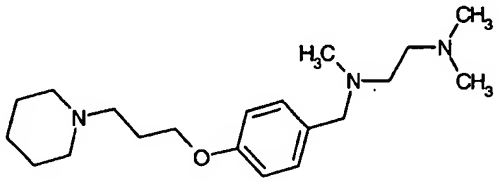
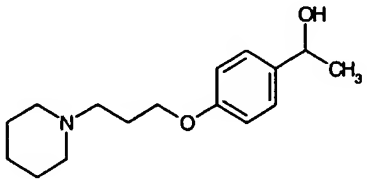
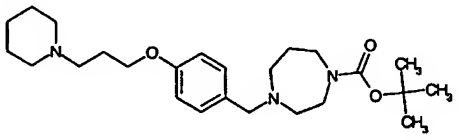
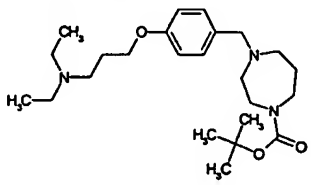
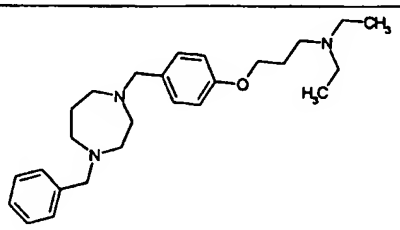
	77		320	
	78		474	
	79		360	
	80		292	
	81		346	
	82		326	
	83		326	

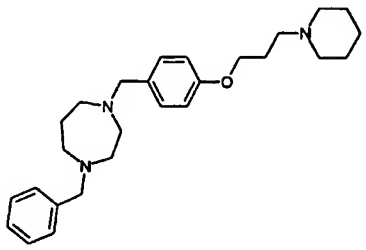
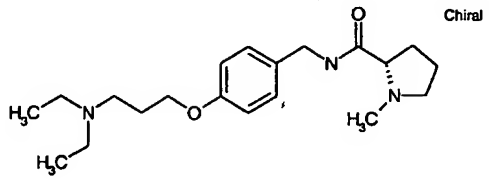
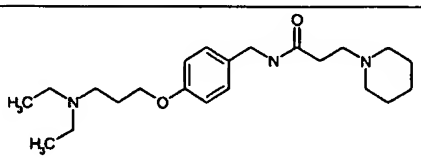
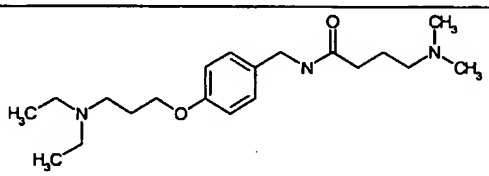
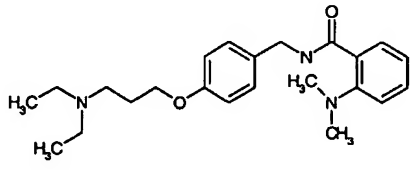
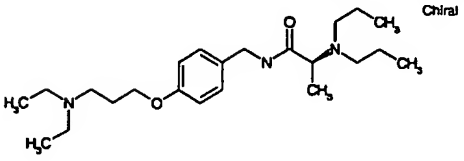
	84			
	85		246	
	86		346	
	87		322	
	88		336	
	89		272	

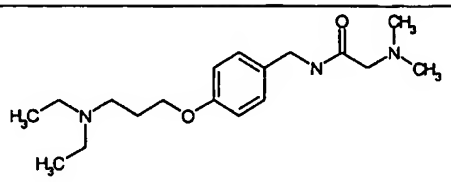
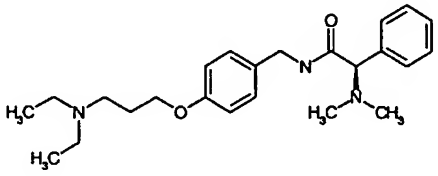
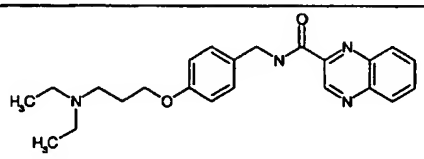
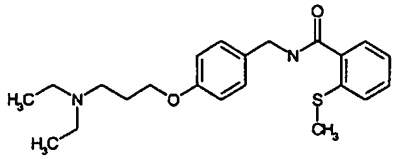
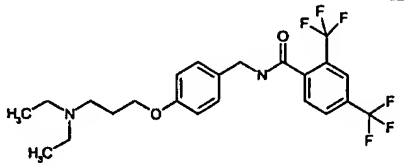
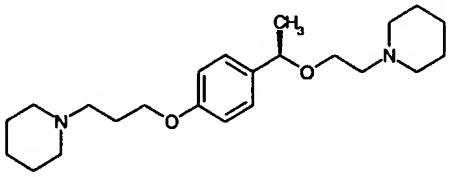
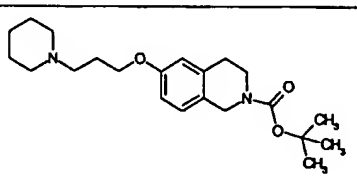
	90		258	
	91		348	
	92		334	
	93		322	
	94		362	
	95		348	

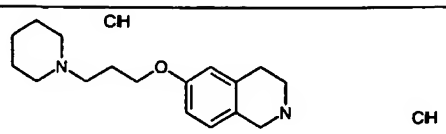
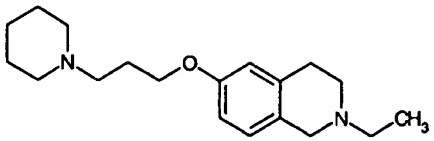
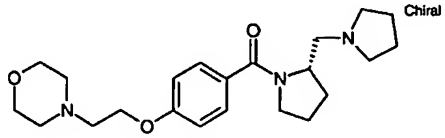
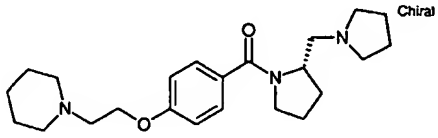
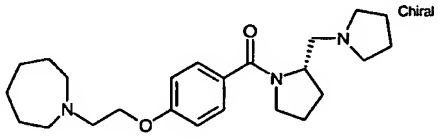
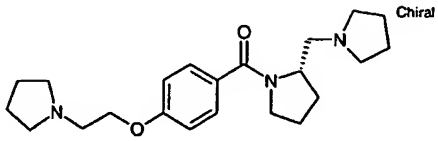
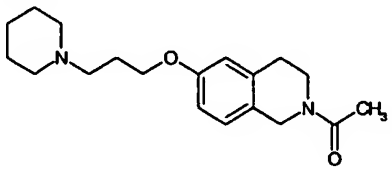
	96		335	
	97		363	
	98		333	
	99		393	
	100		334	
	101		361	
	102		346	

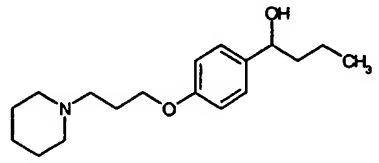
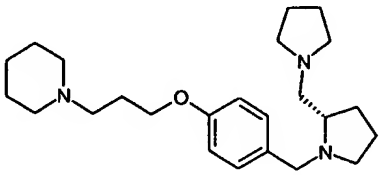
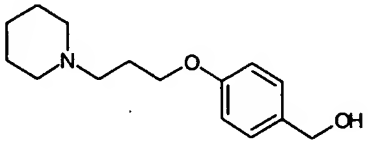
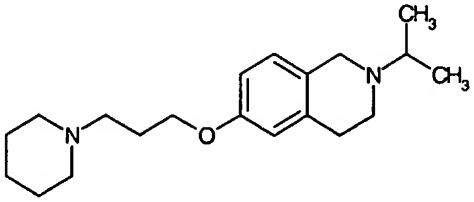
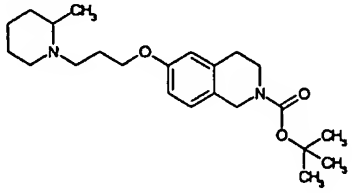
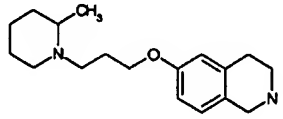
	103		334	
	104		320	
	105		332	
	106		346	
	107		334	
	108		375	

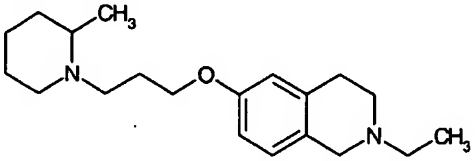
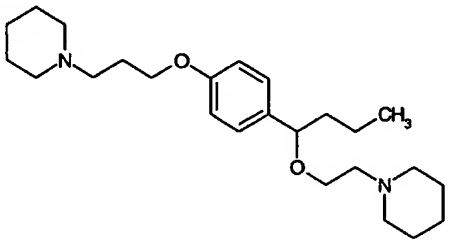
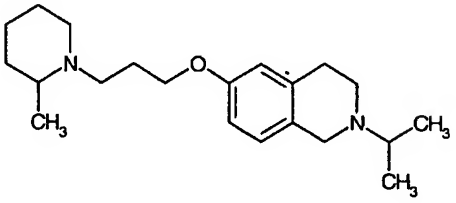
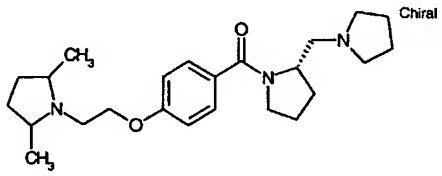
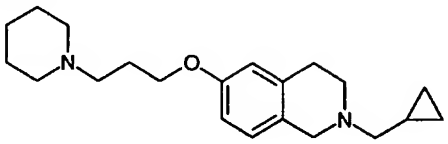
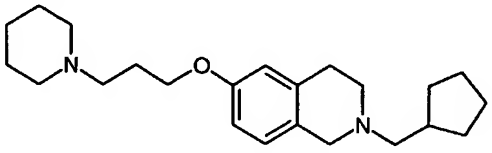
	109		389	
	110		334	
	111		364.1	
	112		432	
	113		420	
	114		410	

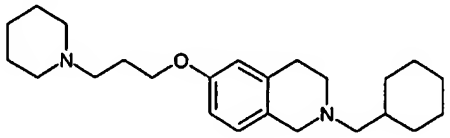
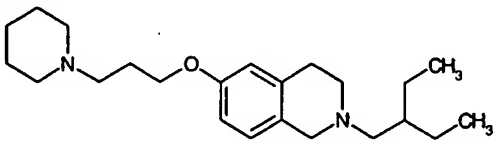
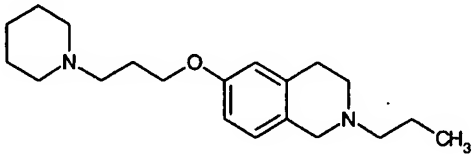
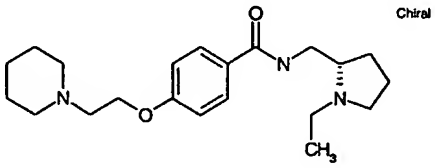
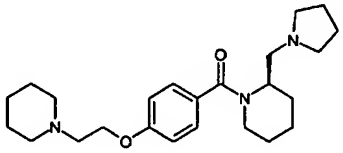
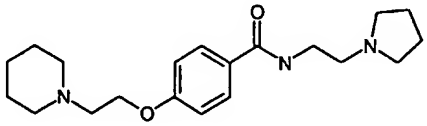
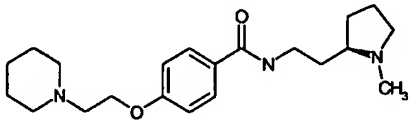
	115		410	
	116		348	
	117		376	
	118		350	
	119		384	
	120		391	

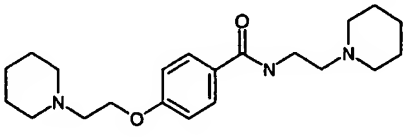
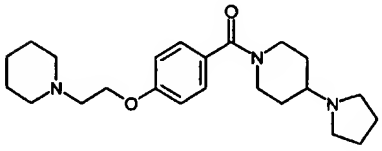
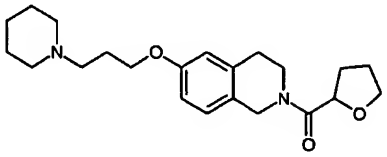
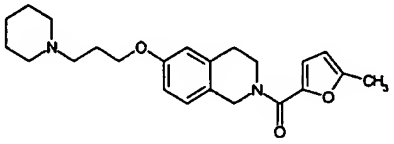
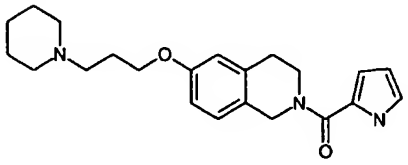
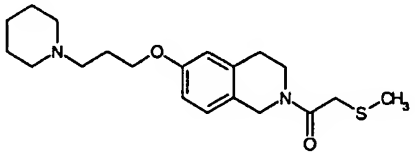
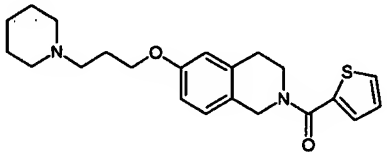
	121		322	
	122		398	
	123		393	
	124		388	
	125		477	
	126		375	
	127		375	

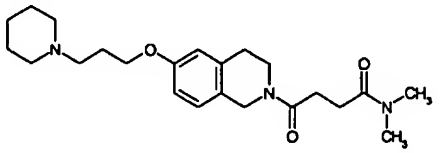
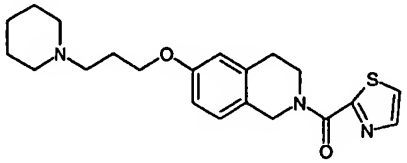
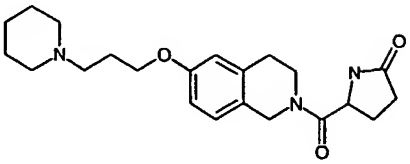
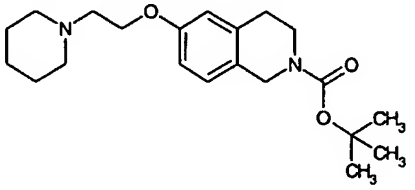
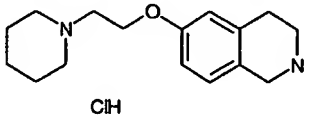
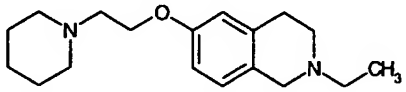
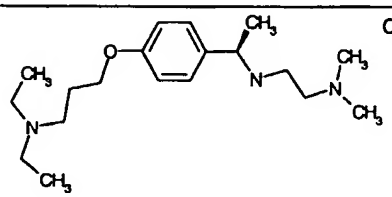
	128		275	
	129		303	
	130		386	
	131		386	
	132		401	
	133		372	
	134		315	

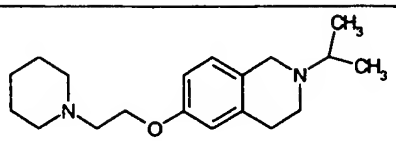
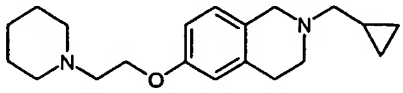
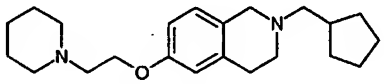
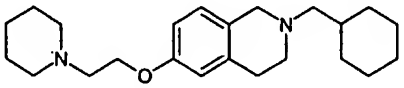
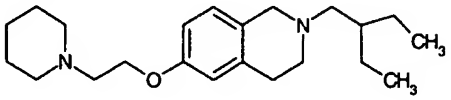
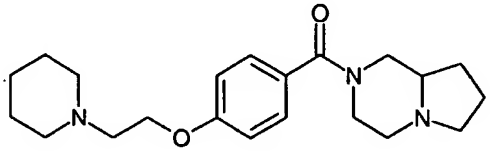
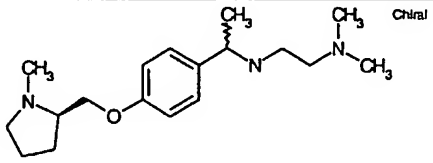
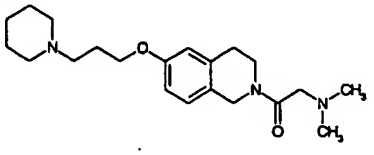
	135		292	
	136		386	
	137		250	
	138		317	
	139		389	
	140		289	

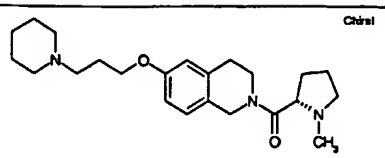
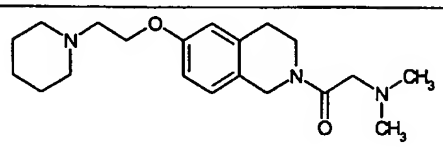
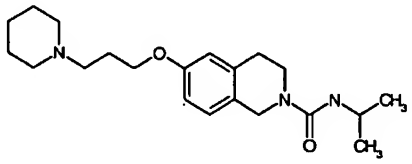
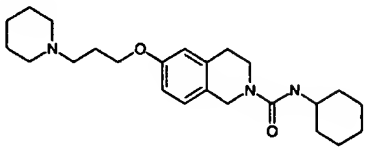
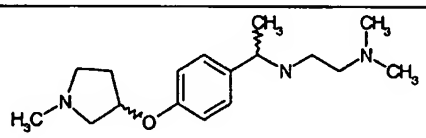
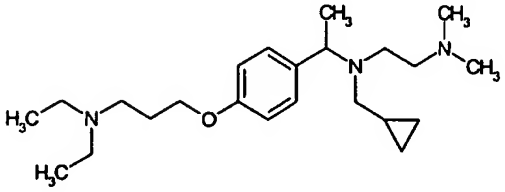
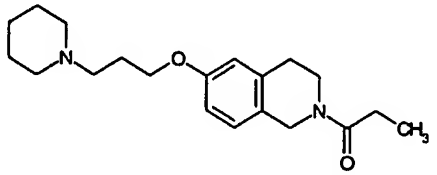
	141		317	
	142		404	
	143		331	
	144		400	
	145		329	
	146		357	

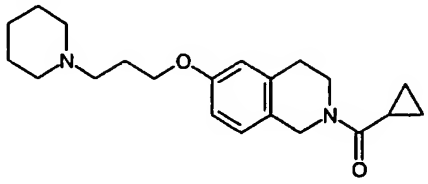
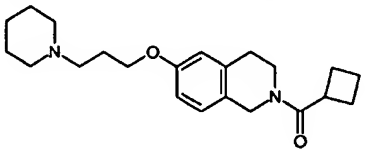
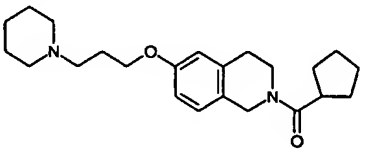
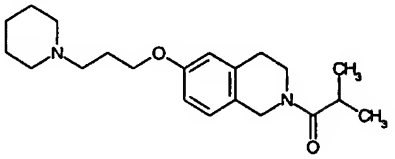
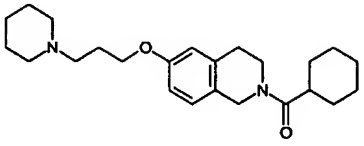
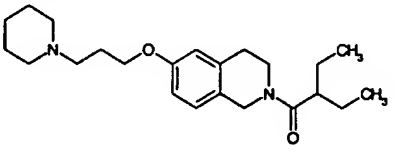
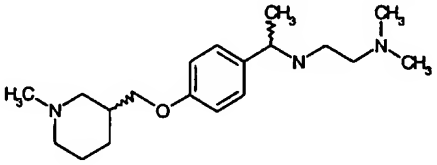
	147		371	
	148		359	
	149		317	
	150		360	
	151		340	
	152		346	
	153		360	

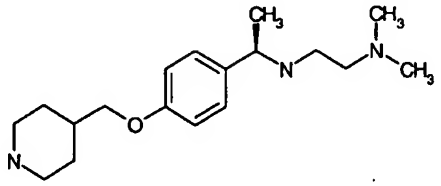
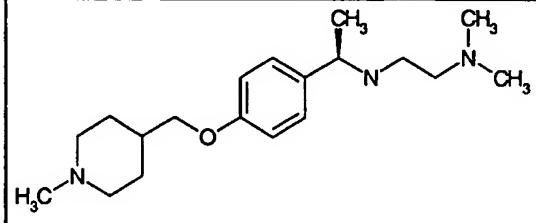
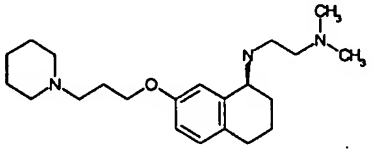
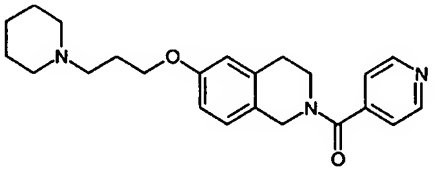
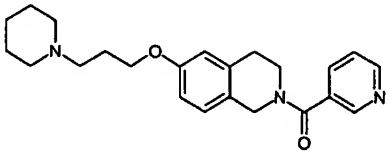
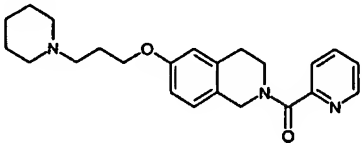
	154		360	
	155		386	
	156		386	
	157		383	
	158		368	
	159		363	
	160		385	

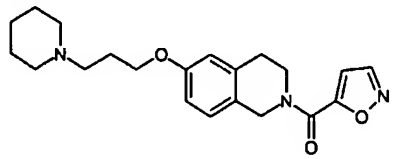
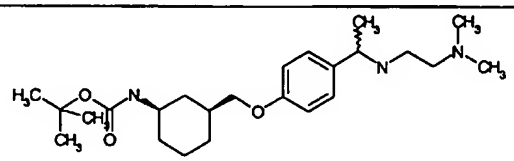
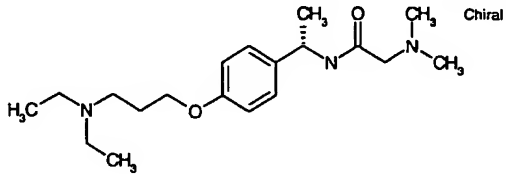
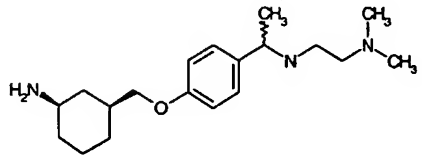
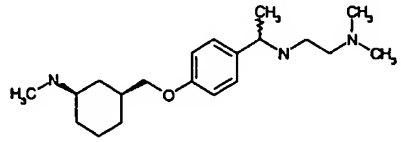
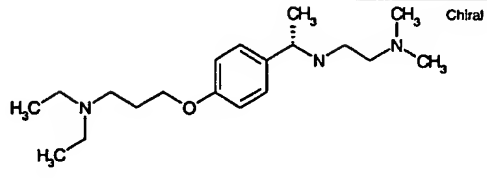
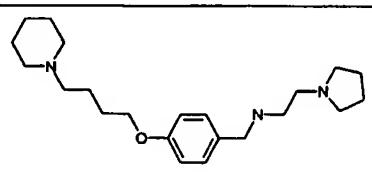
	161		402	
	162		386	
	163		386	
	164		361	
	165	 ClH ClH	261	
	166		289	
	167	 Chiral	322	

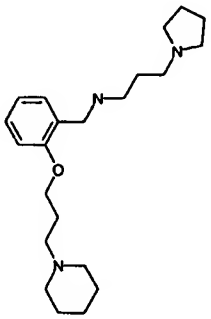
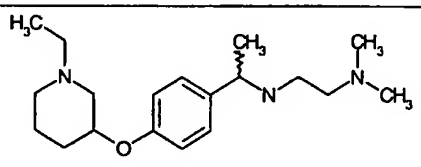
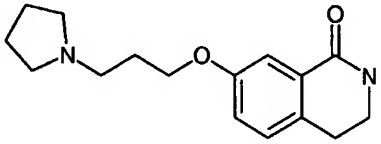
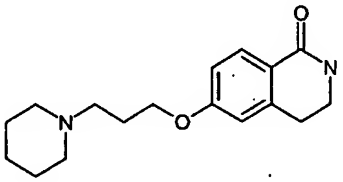
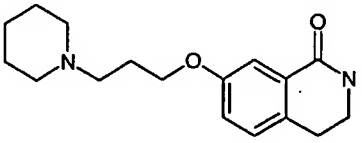
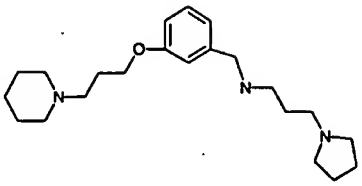
	168		303	
	169		315	
	170		343	
	171		357	
	172		345	
	173		358	
	174		306	
	175		360	

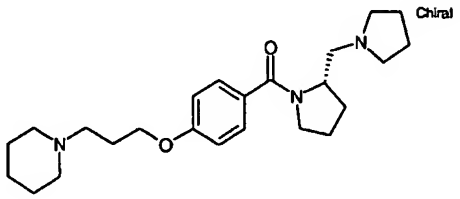
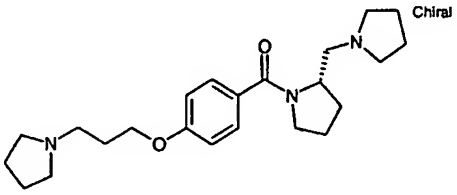
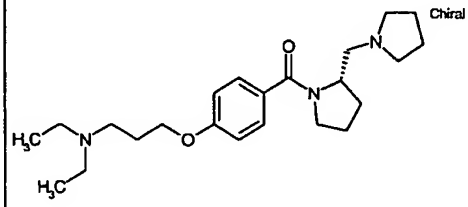
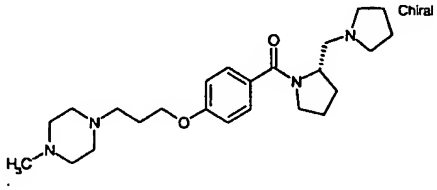
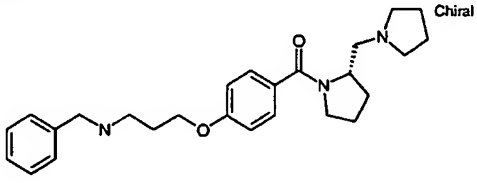
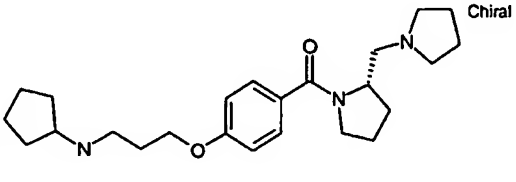
	176		386	
	177		346	
	178		360	
	179		400	
	180		292	
	181		377	
	182		332	

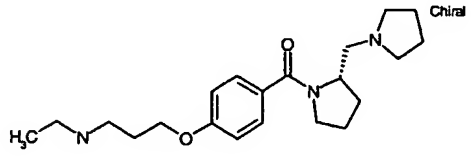
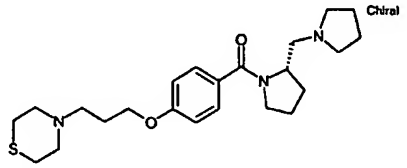
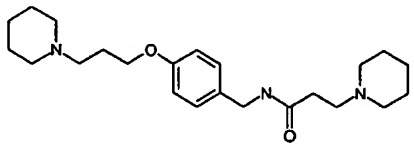
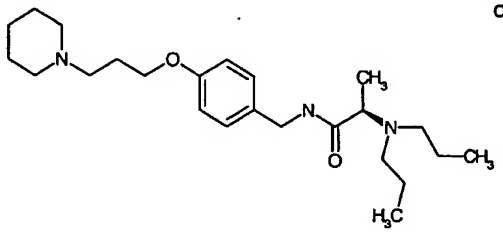
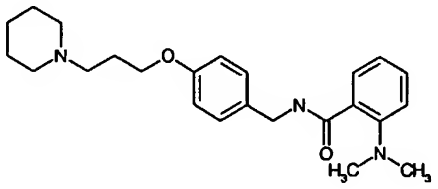
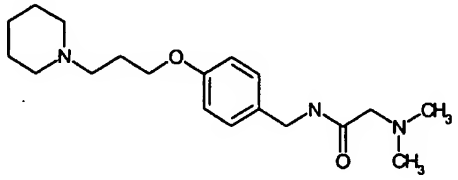
	183		344	
	184		358	
	185		372	
	186		346	
	187		385	
	188		373	
	189		320	

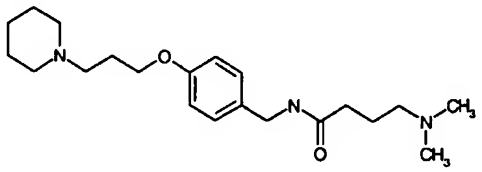
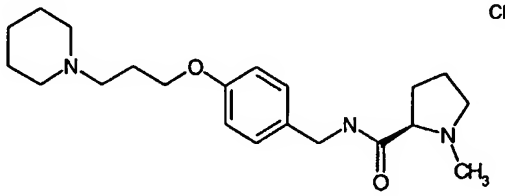
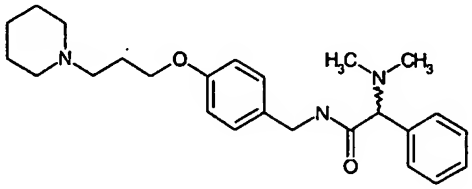
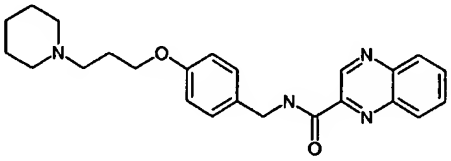
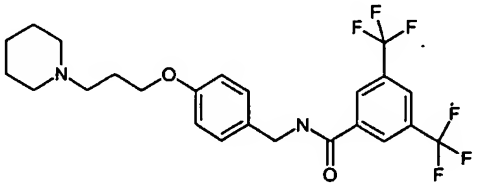
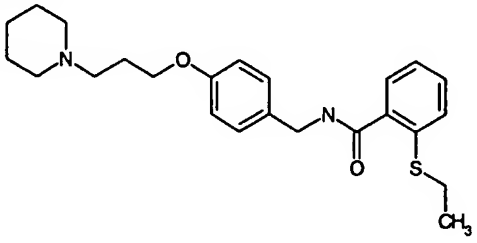
	190		306	
	191		320	
	192		360	
	193		381	
	194		381	
	195		381	

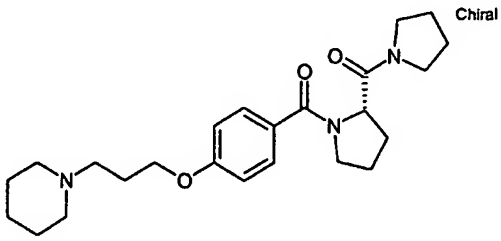
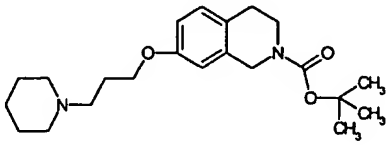
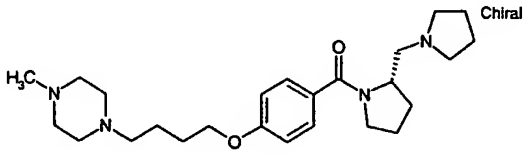
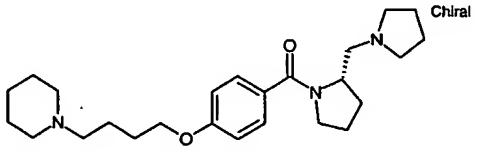
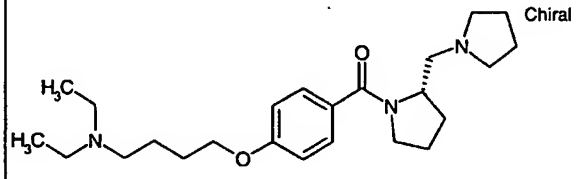
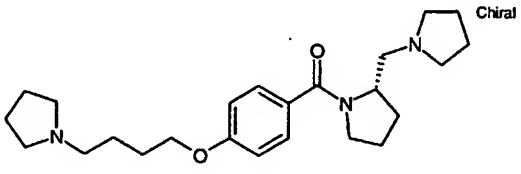
	196		371	
	197		420	
	198		336	
	199		320	
	200		334	
	201		322	
	202		360.4	

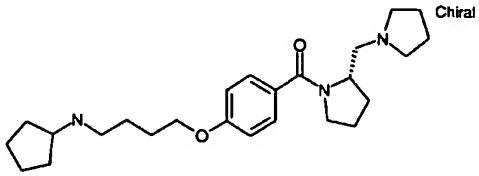
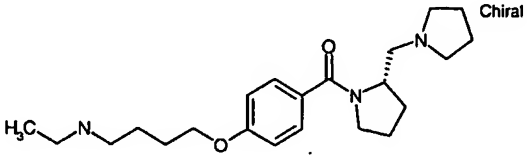
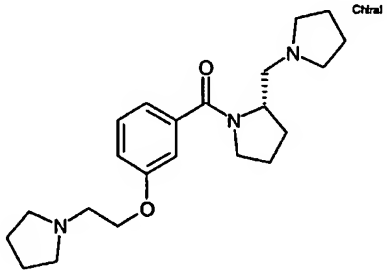
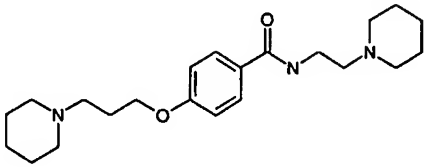
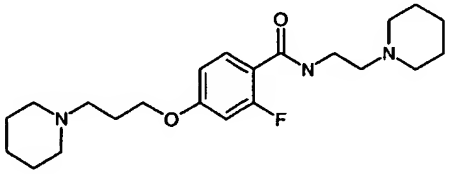
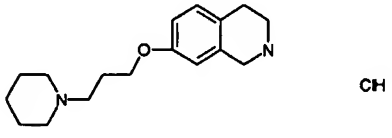
	203		360.2	
	204		360.4	
	205		275.1	
	206		289.1	
	207		289.1	
	208		360.3	

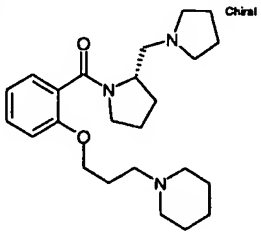
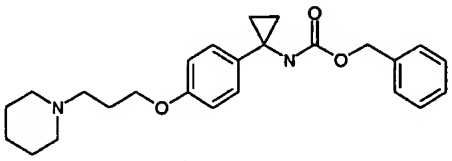
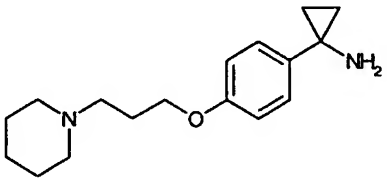
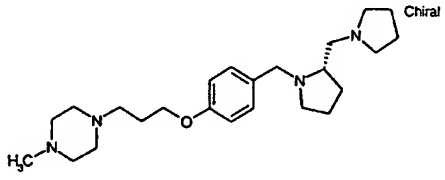
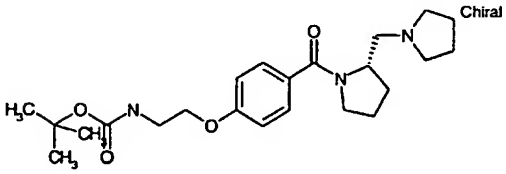
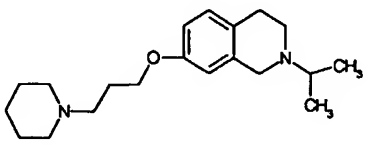
	209		400	
	210		386	
	211		388	
	212		415	
	213		422	
	214		400	

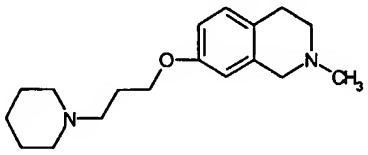
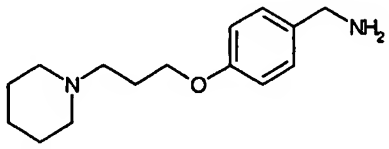
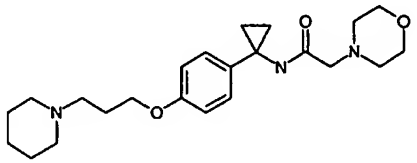
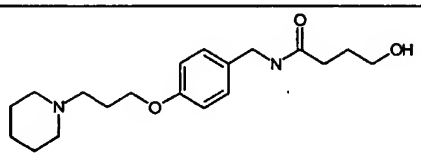
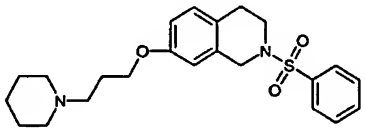
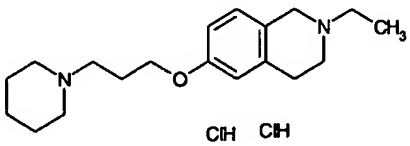
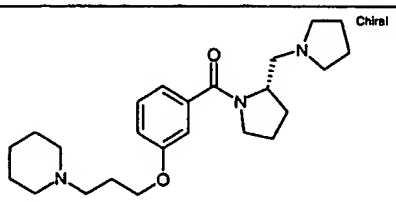
	215		360	
	216		418	
	217		303.3	
	218		404	
	219		395	
	220		334	

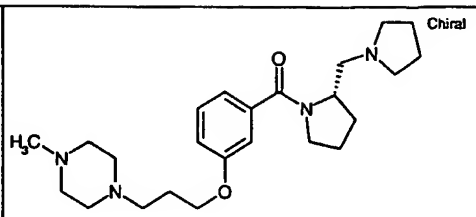
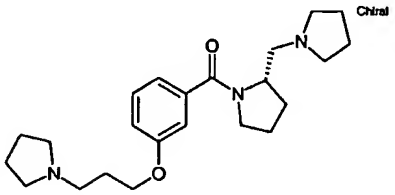
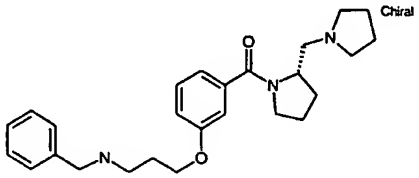
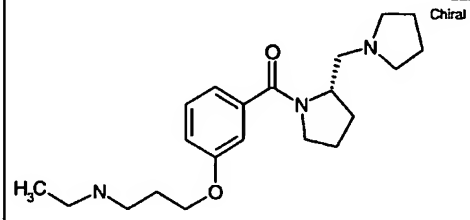
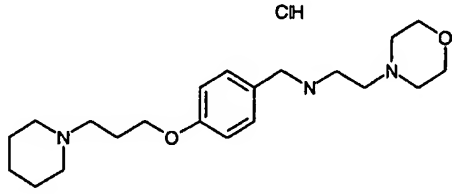
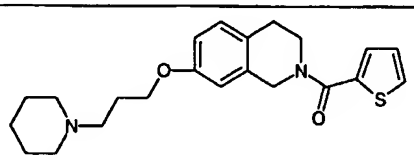
	221		362	
	222	 Chiral	359	
	223		410	
	224		405	
	225		489	
	226		413	

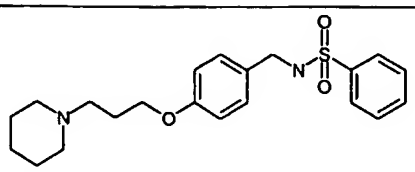
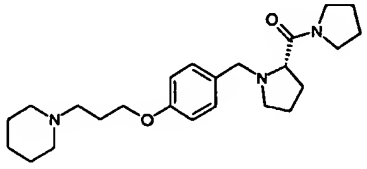
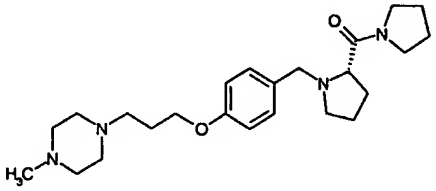
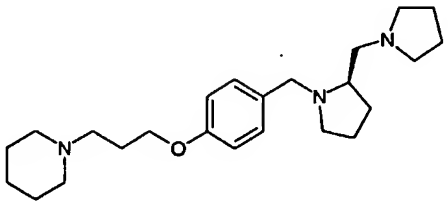
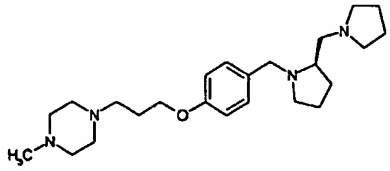
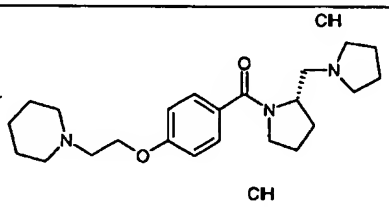
	227		414	
	228		375.3	
	229		429	
	230		414	
	231		402	
	232		400	

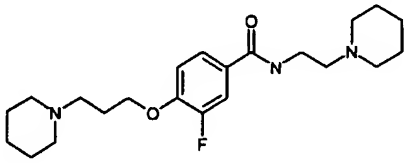
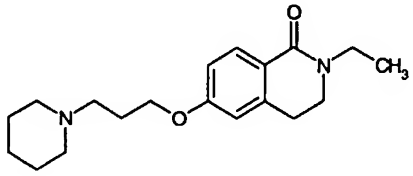
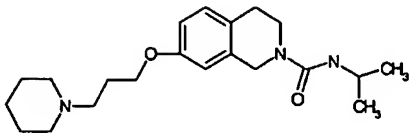
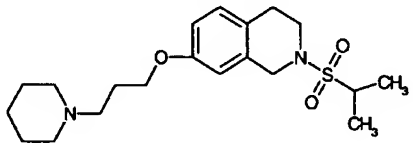
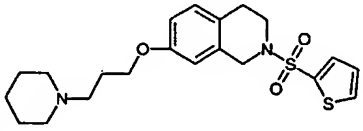
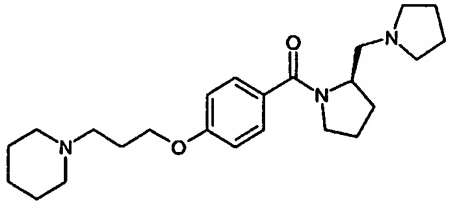
	233		414	
	234		374	
	235		372	
	236		374.3	
	237		329.2	
	238		275.3	

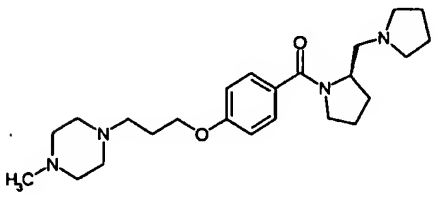
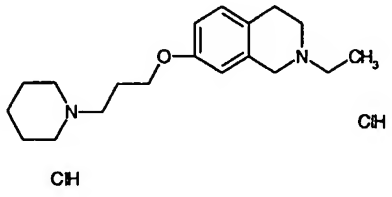
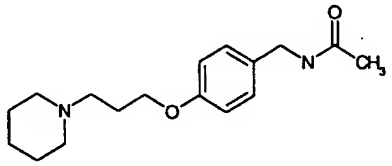
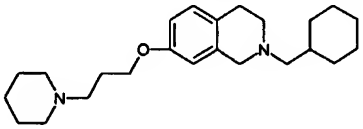
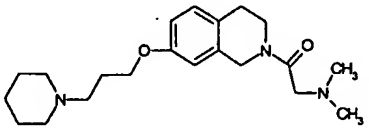
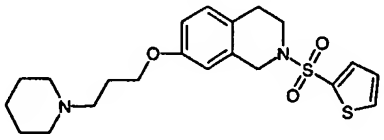
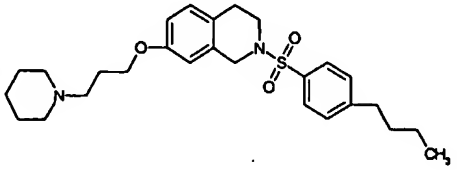
	239		400	
	240		409.3	
	241		275.2	
	242		401	
	243		418	
	244		317.2	

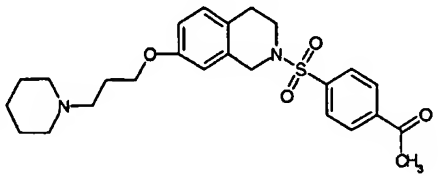
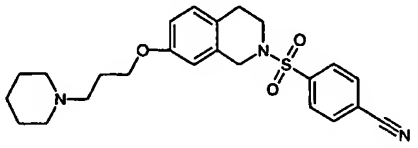
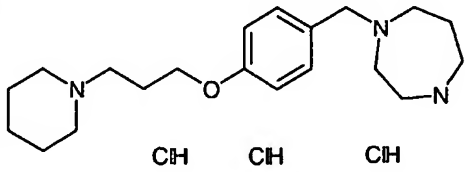
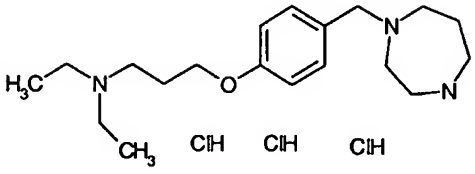
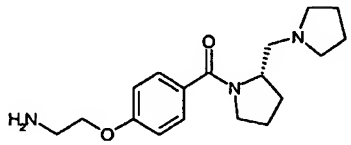
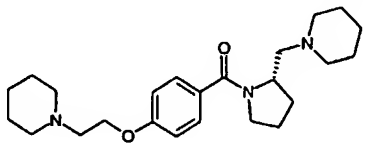
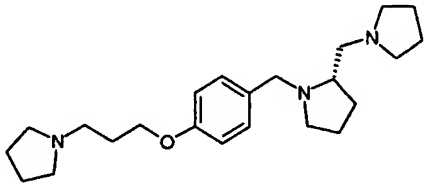
	245		289.1	
	246			
	247		402.3	
	248			
	249		415.1	
	250		303.3	
	251		400	

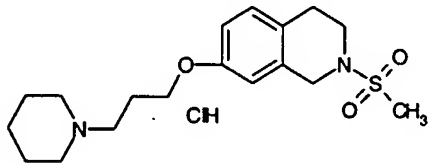
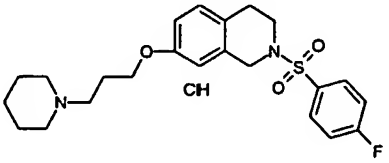
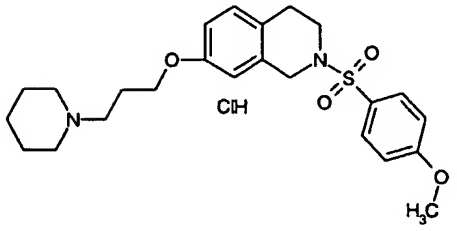
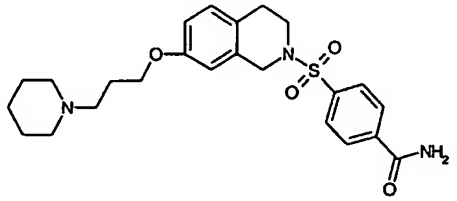
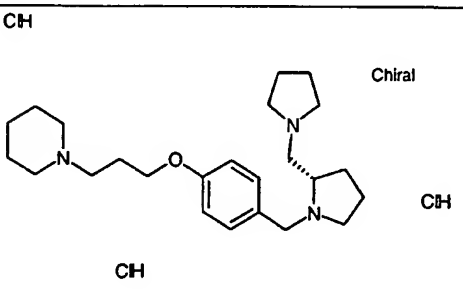
	252		415	
	253		386	
	254		422	
	255		388	
	256		362.2	
	257		385.1	

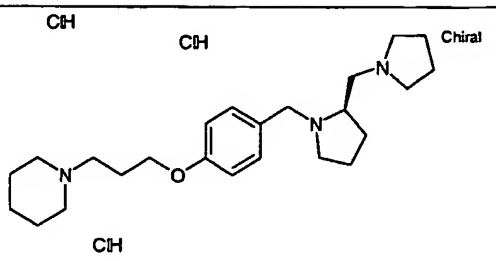
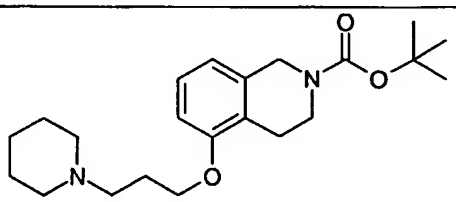
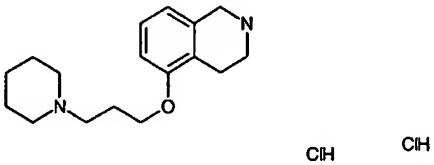
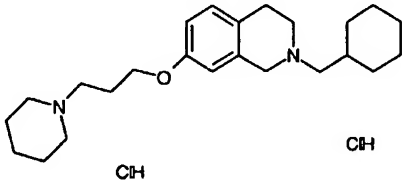
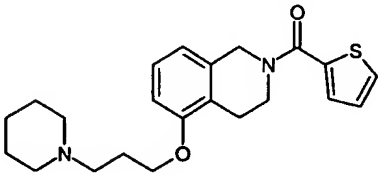
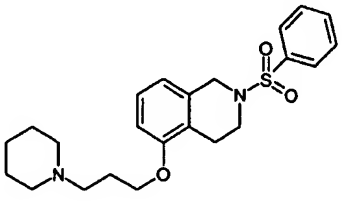
	258			
	259		400	
	260		415	
	261		386	
	262		401	
	263		386	

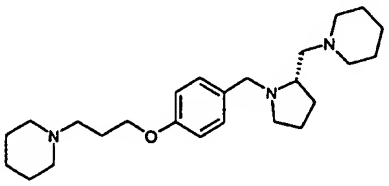
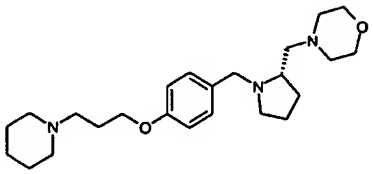
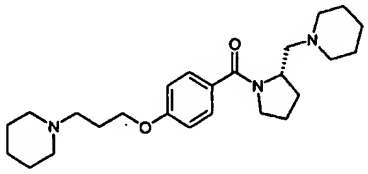
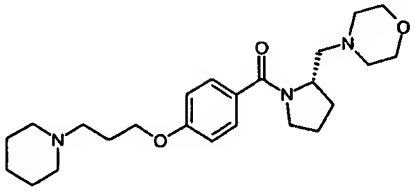
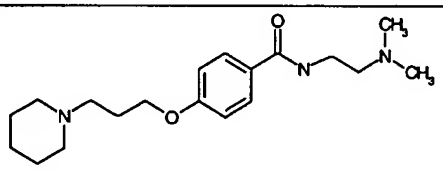
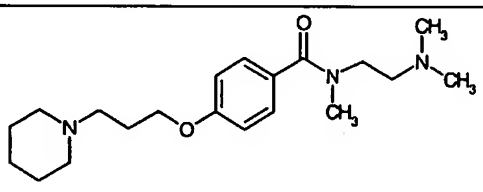
	264		392.2	
	265		317.1	
	266		360.2	
	267		381.1	
	268		421.1	
	269		400	

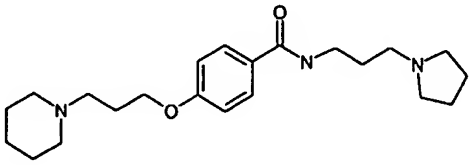
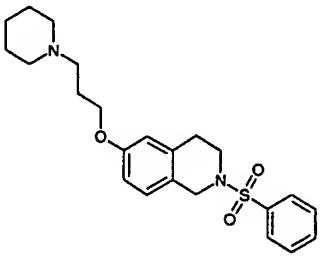
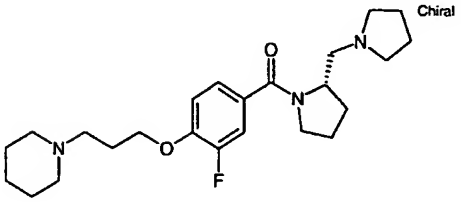
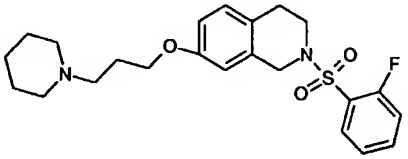
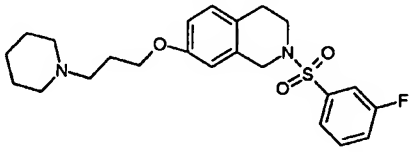
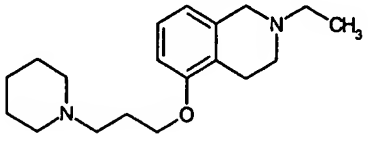
	270		415	
	271		303.3	
	272			
	273		371.4	
	274		360.5	
	275		317.1	
	276		471.1	

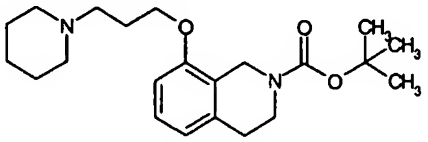
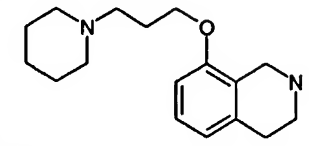
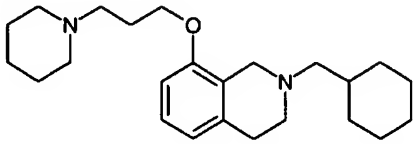
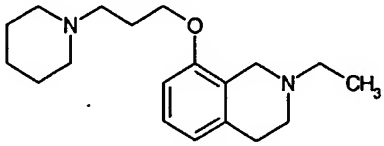
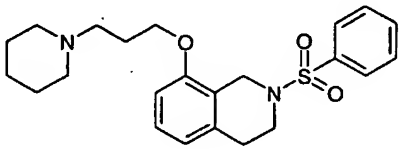
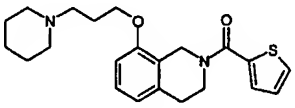
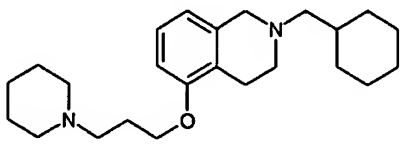
	277		457.1	
	278		440.1	
	279			
	280			
	281		318	
	282		400	
	283		372	

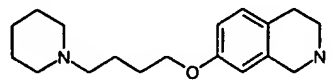
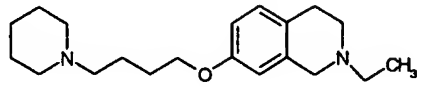
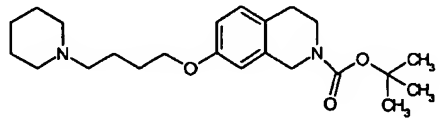
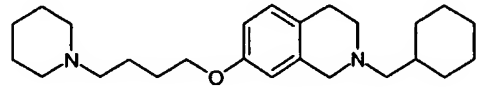
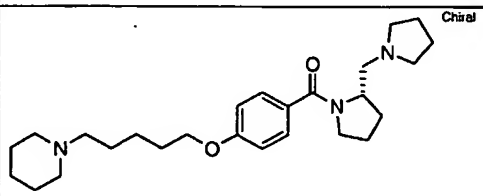
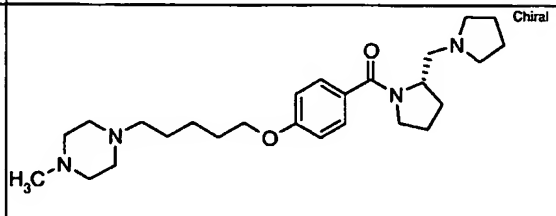
	284		353.2	
	285		433.2	
	286		445.2	
	287		458.2	
	288		386	

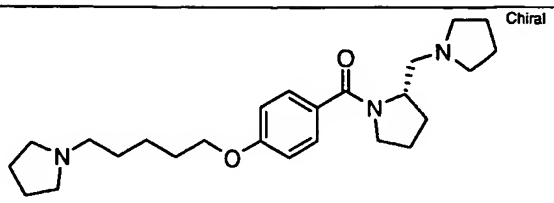
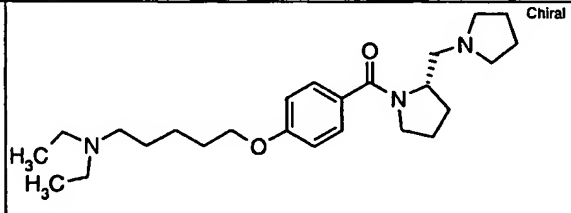
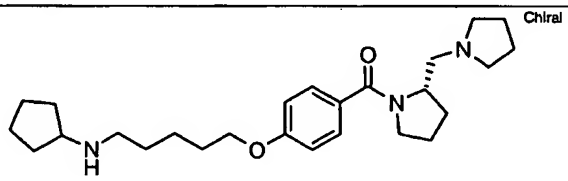
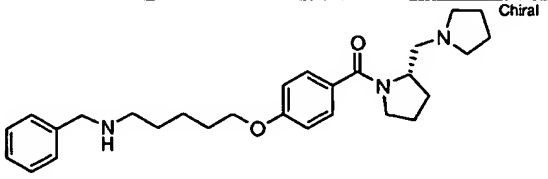
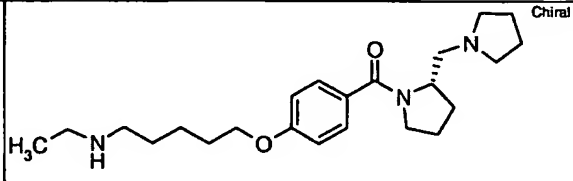
	289		386	
	290		375.3	
	291		275.2	
	292		371.4	
	293		415.2	
	294		385.2	

	295		400	
	296		402	
	297		414	
	298		416	
	299		334	
	300		348	

	301		374	
	302		415.3	
	303		418.4	
	304		433.2	
	305		433.2	
	306		303.3	

	307		375.3	
	308		275.3	
	309		371.4	
	310		303.3	
	311		415.3	
	312		385.3	
	313		371.4	

	314	 CIH CIH	389.3	
	315	 CIH CIH	317.2	
	316		389.3	
	317	 CIH CIH	385.3	
	318	 Chiral	428	
	319	 Chiral	443	

	320	 Chiral	414	
	321	 Chiral	416	
	322	 Chiral	428	
	323	 Chiral	450	
	324	 Chiral	388	

The compound of Formula I is preferably formulated in a unit dosage form prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical composition comprising a compound of Formula I and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (Formula I compound) will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material that acts as a vehicle, excipient, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e., antihistaminic activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration, Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as a re conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 0.01 milligrams to about 1,000 milligrams, preferably from about 0.01 to about 950 milligrams, more preferably from about 0.01 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques

are well known to those skilled in the art. Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day.

Utility

Compounds of Formula I are effective as histamine H3 receptor antagonists. More particularly, these compounds are selective histamine H3 receptor antagonists that have little or no affinity for histamine receptor GPRv53(H4R). As selective antagonists, the compounds of Formula I are useful in the treatment of diseases, disorders, or conditions responsive to the inactivation of the histamine H3 receptor, including but not limited to obesity and other eating-related disorders. It is postulated that selective antagonists of H3R will raise brain histamine levels and possibly that of other monoamines resulting in inhibition of food consumption while minimizing peripheral consequences. Although a number of H3R antagonists are known in the art, none have proven to be satisfactory obesity drugs. There is increasing evidence that histamine plays an important role in energy homeostasis. Histamine, acting as a neurotransmitter in the hypothalamus, suppressed appetite. Histamine is an almost ubiquitous amine found in many cell types and it binds to a family of G protein-coupled receptors (GPCRs). This family provides a mechanism by which histamine can elicit distinct cellular responses based on receptor distribution. Both the H1R and H2R are widely distributed. H3R is primarily expressed in the brain, notably in the thalamus and caudate nucleus. High density of expression of H3R was found in feeding center of the brain. A novel histamine receptor GPRv53 has been recently identified. GPRv53 is found in high levels in peripheral white blood cells; only low levels have been identified in the brain by some investigators while others cannot detect it in the brain. However, any drug discovery effort initiated around H3R must consider GPRv53 as well as the other subtypes.

The inventive compounds can readily be evaluated by using a competitive inhibition Scintillation Proximity Assay (SPA) based on a H3R binding assay using [3H] α methylhistamine as ligand. Stable cell lines, including but not limited to HEK can be transfected with cDNA coding for H3R to prepare membranes used for the binding assay. The technique is illustrated below (Example 3) for the histamine receptor subtypes.

Membranes isolated as described in Example 3 were used in a [35S]GTPχS functional assay. Binding of [35S]GTPχS to membranes indicates agonist activity. Compounds of the invention of Formula I were tested for their ability to inhibit binding in

the presence of agonists. Alternately, the same transfected cell lines were used for a cAMP assay wherein H3R agonists inhibited forskolin-activated synthesis of cAMP. Compounds of Formula I were tested for their ability to permit forskolin –stimulated cAMP synthesis in the presence of agonist.

Preparation of Histamine Receptor Subtype Membranes

A. Preparation H1R membranes

cDNA for the human histamine 1 receptor (H1R) was cloned into a mammalian expression vector containing the CMV promoter (pcDNA3.1(+), Invitogen) and transfected into HEK293 cells using the FuGENE Tranfection Reagent (Roche Diagnostics Corporation). Transfected cells were selected using G418 (500 μ/ml). Colonies that survived selection were grown and tested for histamine binding to cells grown in 96-well dishes using a scintillation proximity assay (SPA) based radioligand binding assay. Briefly, cells, representing individual selected clones, were grown as confluent monolayers in 96-well dishes (Costar Clear Bottom Plates, #3632) by seeding wells with 25,000 cells and growing for 48 hours (37°C, 5% CO_2). Growth media was removed and wells were rinsed two times with PBS (minus Ca^{2+} or Mg^{2+}). For total binding, cells were assayed in a SPA reaction containing 50mM Tris-HCL (assay buffer), pH 7.6, 1mg wheat germ agglutinin SPA beads (Amersham Pharmacia Biotech, #RPNQ0001), and 0.8nM ^{3}H-pyrilamine (Net-594, NEN) (total volume per well = 200μl). Astemizole (10μM, Sigma #A6424) was added to appropriate wells to determine non-specific binding. Plates were covered with FasCal and incubated at room temperature for 120 minutes. Following incubation, plates were centrifuged at 1,000rpm (~800g) for 10 minutes at room temperature. Plates were counted in a Wallac Trilux 1450 Microbeta scintillation counter. Several clones were selected as positive for binding, and a single clone (H1R40) was used to prepare membranes for binding studies. Cell pellets, representing ~10 grams, were resuspended in 30ml assay buffer, mixed by vortexing, and centrifuged (40,000g at 4°C) for 10 minutes. The pellet resuspension, vortexing, and centrifugation was repeated 2 more times. The final cell pellet was reusupened in 30ml and homogenized with a Polytron Tissue Homogenizer. Protein determinations were done using the Coomassie Plus Protein Assay Reagent (Pierce). Five micrograms of protein was used per well in the SPA receptor-binding assay.

B. Preparation H2R membranes

cDNA for the human histamine 2 receptor was cloned, expressed and transfected into HEK 293 cells as described above. Histamine binding to cells was assayed by SPA described above. For total binding, cells were assayed in a SPA reaction containing 50mM Tris-HCl (assay buffer), pH 7.6, 1mg wheat germ agglutinin SPA beads (Amersham Pharmacia Biotech, #RPNQ0001), and 6.2nM ^{3}H-tiotidine (Net-688, NEN) (total volume per well = 200µl). Cimetidine (10µM, Sigma #C4522) was added to appropriate wells to determine non-specific binding.

Several clones were selected as positive for binding, and a single clone (H2R10) was used to prepare membranes for binding studies. Five micrograms of protein was used per well in the SPA receptor-binding assay.

C. Preparation of H3R membranes

cDNA for the human histamine 3 receptor was cloned and expressed as described in Example 1, above. Transfected cells were selected using G418 (500 µ/ml), grown, and tested for histamine binding by the SPA described above. For total binding, cells were assayed in a SPA reaction described above containing 50mM Tris-HCL (assay buffer), pH 7.6, 1mg wheat germ agglutinin SPA beads (Amersham Pharmacia Biotech, #RPNQ0001), and 1nM (^{3}H)-n-alpha-methylhistamine (NEN, NET1027) (total volume per well = 200µl). Thioperimide was added to determine non-specific binding. Several clones were selected as positive for binding, and a single clone (H3R8) was used to prepare membranes for binding studies described above. Five micrograms of protein was used per well in the SPA receptor-binding assay.

All compounds set forth in examples 1 to 322 exhibited affinity for the H3 receptor greater than 1 uM. Preferred compounds of the invention exhibited affinity for the H3 receptor greater than 200 nM. Most preferred compounds of the invention exhibit affinity for the H3 receptor greater than 20 nM.

D. Preparation of GPRv53 Membranes

cDNA for the human GPRv53 receptor was cloned and expressed as described in Example 1, above. Transfected cells were selected, tested for histamine binding, and selected. HEK293 GPRv53 50 cells were grown to confluency in DMEM/F12 (Gibco)

supplemented with 5 % FBS and 500 ug/ml G418 and washed with Delbecco's PBS (Gibco) and harvested by scraping. Whole cells were homogenized with a Polytron tissuemizer in binding buffer, 50 mM Tris pH 7.5. Cell lysates, 50 ug, were incubated in 96 well dishes with 3 nM (3H) Histamine and compounds in binding buffer for 2 hours at room temperature. Lysates were filtered through glass fiber filters (Perkin Elmer) with a Tomtec cell harverster. Filters were counted with melt-on scintillator sheets (Perkin Elmer) in a Wallac Trilux 1450 Microbeta Scintillation counter for 5 minutes.

Pharmacological Results

cAMP ELISA

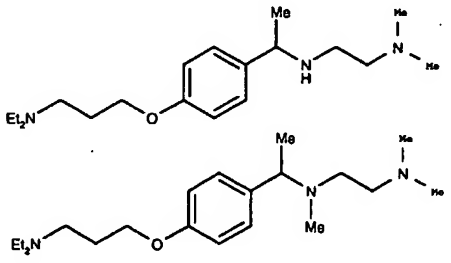
HEK293 H3R8 cells prepared as described above were seeded at a density of 50,000 cells/well and grown overnight in DMEM/F12 (Gibco) supplemented with 5 % FBS and 500 ug/ml G418. The next day tissue culture medium was removed and replaced with 50 µl cell culture medium containing 4 mM 3-isobutyl-1-methylxanthine (Sigma) and incubated for 20 minutes at room temperature. Antagonist were added in 50 µl cell culture medium and incubated for 20 minutes at room temperature. Agonist R (-)α methylhistamine (RBI) at a dose response from $1x10^{-10}$ to $1x10^{-5}$ M was then added to the wells in 50 µl cell culture medium and incubated for 5 minutes at room temperature. Then 50 µl of cell culture medium containing 20 µM Forskolin (Sigma) was added to each well and incubated for 20 minutes at room temperature. Tissue culture medium was removed and cells were lysed in 0.1M HCl and cAMP was measured by ELISA (Assay Designs, Inc.).

[35S] GTP γ [S] Binding Assay

Antagonist activity of selected compounds was tested for inhibition of [35S] GTP γ [S] binding to H3R membranes in the presence of agonists. Assays were run at room temperature in 20 mM HEPES, 100 mM NaCl ,5 mM $MgCl_2$ and 10 uM GDP at pH 7.4 in a final volume of 200 ul in 96-well Costar plates. Membranes isolated from H3R8-expressing HEK293 cell line (20 ug/well) and GDP were added to each well in a volume of 50 µl assay buffer. Antagonist was then added to the wells in a volume of 50 µl assay buffer and incubated for 15 minutes at room temperature. Agonist R(-)alpha

methylhistamine (RBI) at either a dose response from $1x10^{-10}$ to $1x10^{-5}$ M or fixed concentration of 100 nM were then added to the wells in a volume of 50 µl assay buffer and incubated for 5 minutes at room temperature. GTP γ [35S] was added to each well in a volume of 50 µl assay buffer at a final concentration of 200 pM, followed by the addition of 50 µl of 20 mg/ml WGA coated SPA beads (Amersham). Plates were counted in Wallac Trilux 1450 Microbeta scintillation counter for 1 minute. Compounds that inhibited more than 50% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K[i](nM). The results are given below the indicated compound.

Table 1

Compound	Ki (nM)	Structure
Example 2	1.48, 0.95	
Example 1	1.4	

To investigate the selectivity of the antagonists for the histamine receptors, a competitive binding assay described above was performed. The ability of example 131and 250 (structures given above) to selectively inhibit binding to H3R, H1R, H2 and H4R was determined. Importantly, the identification of H3R-specific antagonists that do bind the newly identified H4R was demonstrated. Until the present invention, most known H3R antagonists also bound H4R. As demonstrated in Table 2, example 131 and example 250 did not inhibit binding H4R compare to H3R. To our knowledge, the study in Table 2 is the first demonstration of a H3R specific antagonist.

Table 2

Ki (nM)

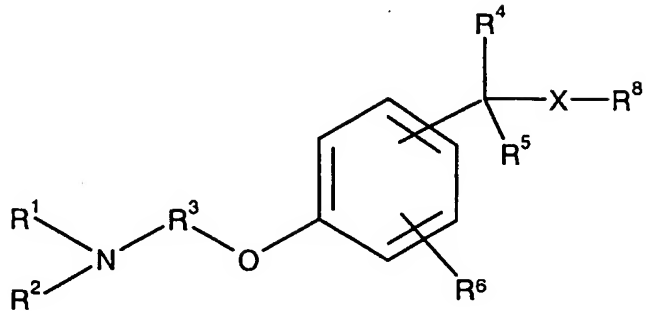
Compound	H3R	H4R	H1R	H2
Example 131	1.05	≥ 20,000	≥ 20,000	≥ 20,000
Example 250	0.37	≥ 20,000	1022	1109

Non-imidazole containing histamine H3 receptor antagonists disclosed in the literature generally have very poor pharmacokinetic properties (see J. Apelt, et al, J. Med. Chem. 2002, 45, 1128-1141). Compounds of this invention have markedly and unexpectedly improved pharmacokinetic properties. Male Sprague Dawley Rats (n=3 per dose arm) were separately dosed with 3 mg/kg iv or 10 mg/kg po of compound examples 131 and 271 (vehicle: 5% ethanol/water or water respectively; dose volume: 1 mL/kg iv, 10 mL/kg po). Approximately 0.5 mL of blood was collected in heparin collection tubes at multiple time points over an 8 or 24-hour period for examples 131 and 271 respectively, and the samples were analyzed using LC/MS/MS. In this manner compound example 131 was found to have an oral bioavailability of 58% (AUC 0-24hr; po/iv ratio) and an oral half-life of 10.4 ± 4.2 hours (±SEM). Compound example 271 was found to have an oral bioavailability of 69% (AUC 0-24hr; po/iv ratio) and an oral half-life of 71.9 ± 3.3 hours (±SEM).

From the above description, one skilled in the art can ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

WHAT IS CLAIMED IS:

1. A compound structurally represented by Formula I



or pharmaceutically acceptable salts thereof wherein:

X is O, NR^7 or S;

R^1 is hydrogen,

C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,

$(CHR^5)_n$-C_3-C_7 cycloalkyl,

$(CHR^5)_n$ aryl,

$(CHR^5)_n$ heteroaryl, or

$(CHR^5)_n$-O$(CHR^5)_n$-aryl;

R^2 is independently R^1, or

COR^1 , or cyclized with the attached nitrogen atom at the R^1 position to form a 4, 5, or 6 member carbon ring, wherein one of said carbons is optionally replaced by one of O, S, NR^1 or CO, or wherein the ring formed by R^1 and R^2 is optionally substituted one to two times with C_1-C_4 alkyl;

R^3 is independently C_3-C_7 cycloalkylene, or C_1- C_4 alkylene optionally substituted;

R^4 is hydrogen,
halogen,
C_1-C_4 alkyl,
$(CHR^5)_n$-C_3-C_7 cycloalkyl,
$(CHR^5)_n$ aryl,
$(CHR^5)_n$ heteroaryl,
$(CHR^5)_n$-$O(CHR^5)_n$-aryl or
CO or
cyclized with R^5 to from a cyclopropyl ring;

R^5 is hydrogen , or
C_1-C_4 alkyl;

R^6 is hydrogen,
halo or
cyclized with the attached carbon atom at the R^5 position to form a 5 to 6 member carbon ring,
cyclized with the attached carbon atom at the R^7 position to form a 5 to 6 member heterocyclic ring or

R^7 is hydrogen,
C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,
$(CHR^5)_n$-C_3-C_7 cycloalkyl,
$(CHR^5)_n$ aryl,
$(CHR^5)_n$ heteroaryl,
$(CHR^5)_n$-$O(CHR^5)_n$-aryl,
SO_2R^1 or

Cyclized with attached carbon on R^8 to from a 5, 6, or 7 membered carbon ring optionally substituted with R^9, CF_3, or CN, optionally one of the said carbons is replaced by N, NR^1, CO;

R^8 is hydrogen,
a bond,
C_1-C_8 alkyl
$-SO_2 R^9$,
$-CO_2 R^{10}$,
$-CO R^9$,
$-CONH R^{10}$;

R^9 is hydrogen,
halogen,
C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,
C_3-C_7 cycloalkyl,
aryl,
CH_2 aryl,
heteroaryl,
heterocycle,
$-O(CHR^5)_n$-aryl,
$-COR^1$,
$-CONR^1 R^2$,
$-SO_2R^1$,
$-OR^1$,
$-N(R^1)_2$,
$-NR^1 R^2$,
$-CH_2NR^1 R^2$,

-$CONR^1R^2$

-$NHSO_2R^1$,

-NO_2,

-CO_2R^1,

-$SO_2N(R^1)_2$,

-$S(O)_nR^1$,

-OCF_3,

-CH2SR^5,

R^{10} is hydrogen,

halogen,

C_1-C_8 alkyl optionally substituted with 1 to 4 halogens,

C_3-C_7 cycloalkyl,

aryl,

CH_2 aryl,

heteroaryl,

heterocycle,

-COR^1,

-$CONR^1R^2$,

-SO_2R^1,

-$N(R^1)_2$,

-NR^1R^2,

-$CH_2NR^1R^2$,

-$CONR^1R^2$

-CO_2R^1,

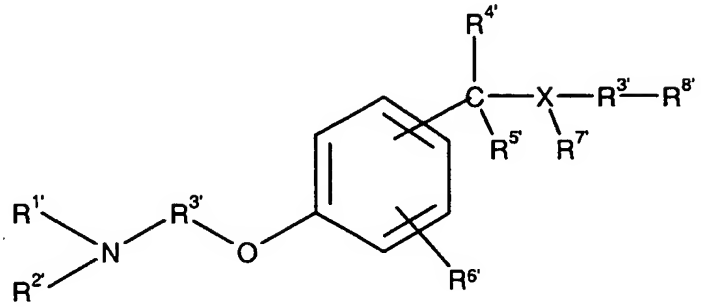
-$SO_2N(R^1)_2$,

-$S(O)_nR^1$,

-CH2SR^5,

and n is 0 - 4.

2. A compound of claim 1, structurally represented by Formula II



or pharmaceutically acceptable salts thereof where:

X is O, N or S;

$R^{1'}$ is hydrogen,

C_1-C_8 alkyl (optionally substituted with 1 to 4 halogens or C_1-C_4 alkyls),

$(CHR^{5'})_n$-C_3-C_7 cycloalkyl,

$(CHR^{5'})_n$ aryl,

$(CHR^{5'})_n$ heteroaryl, or

$(CHR^{5'})_n$-O$(CHR^{5'})_n$-aryl;

$R^{2'}$ is independently $R^{1'}$, or

cyclized with the attached nitrogen atom at the $R^{1'}$ position to form a 5 to 6 member carbon ring (optionally one of said carbons is replaced by one of O, S or N);

$R^{3'}$ is independently C_1- C_4 alkyl;

$R^{4'}$ is hydrogen,
halogen,
C_1-C_4 alkyl,
$(CHR^{5'})_n$-C_3-C_7 cycloalkyl,
$(CHR^{5'})_n$ aryl,
$(CHR^{5'})_n$ heteroaryl,
$(CHR^{5'})_n$-$O(CHR^5)_n$-aryl or
carbonyl;

$R^{5'}$ is hydrogen or C_1-C_4 alkyl;

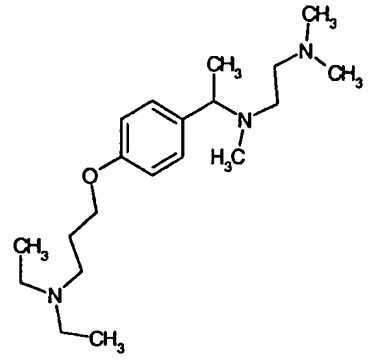
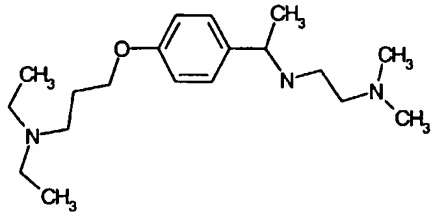
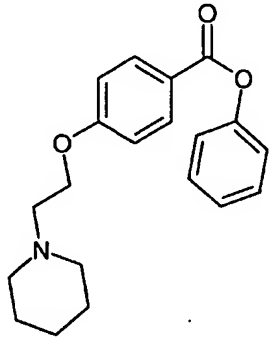
$R^{6'}$ is hydrogen, or
cyclized with the attached carbon atom at the $R^{5'}$ position to form a 5 to 6 member carbon ring, or
cyclized with the attached carbon atom at the $R^{7'}$ position to form a 5 to 6 member heterocyclic ring;

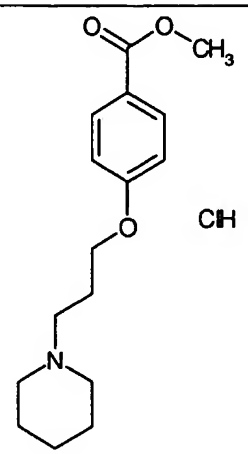
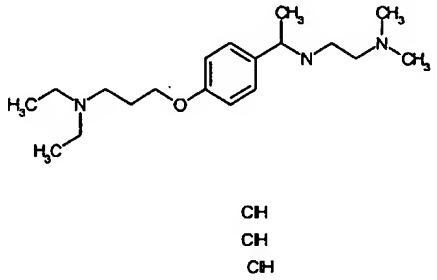
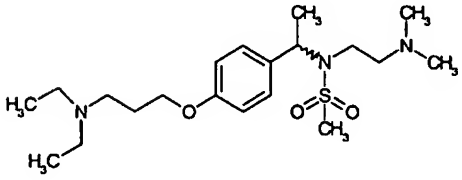
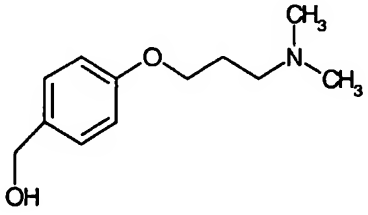
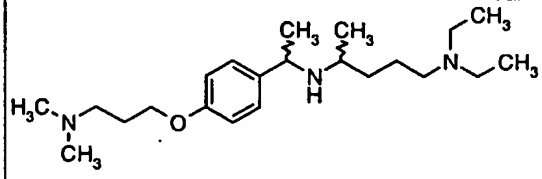
$R^{7'}$ is hydrogen,
C_1-C_8 alkyl (optionally substituted with 1 to 4 halogens or C_1-C_4 alkyls),
$(CHR^{5'})_n$-C_3-C_7 cycloalkyl,
$(CHR^{5'})_n$ aryl,
$(CHR^{5'})_n$ heteroaryl,
$(CHR^{5'})_n$-$O(CHR^{5'})_n$-aryl

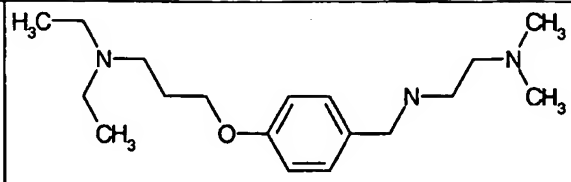
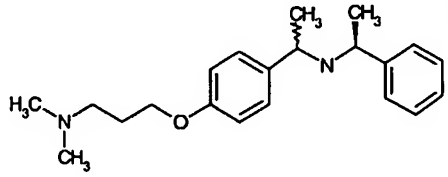
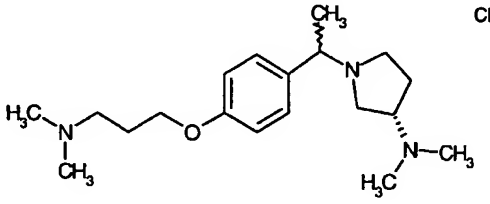
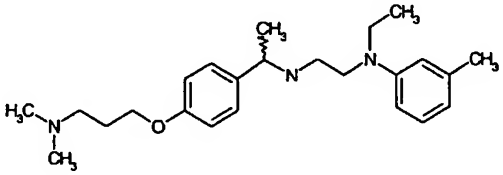
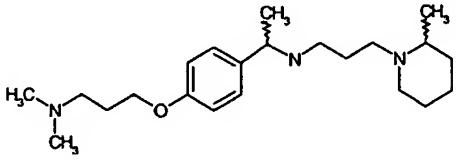
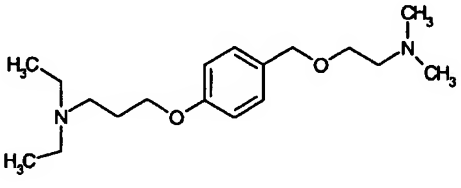
$R^{8'}$ is hydrogen,
halogen,
C_1-C_8 alkyl (optionally substituted with 1 to 4 halogens or C_1-C_4 alkyls),
C_3-C_7 cycloalkyl,

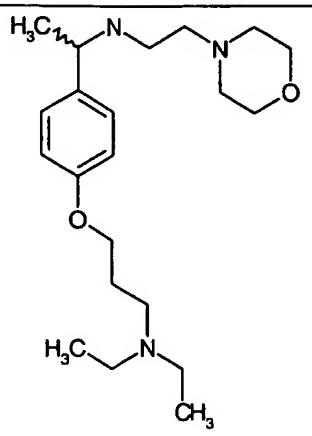
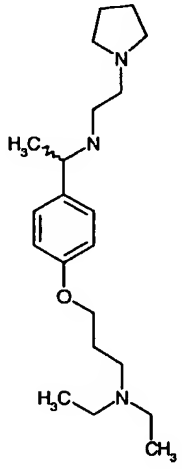
aryl,
heteroaryl,
$-O(CHR^{5'})_n$-aryl,
$-COR^1$,
$-SO_2R^{1'}$,
$-OR^1$,
-CN,
$-CF_3$,
$-N(R^{1'})_2$,
$-NHSO_2R^{1'}$,
$-NO_2$,
$-CO_2R^{1'}$,
$-SO_2N(R^{1'})_2$,
$-S(O)_nR^{1'}$, or
$-OCF_3$; and
n is 0 - 4.

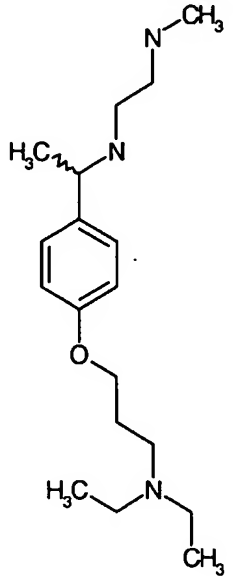
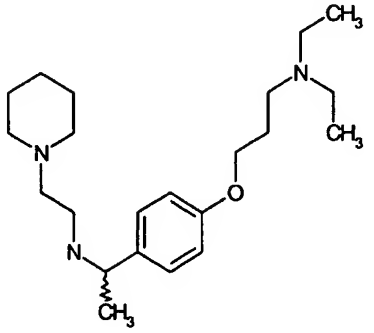
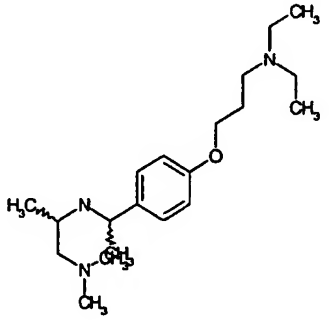
3. The compound of Claim 1, wherein X is nitrogen.
4. The compound of claim 1 or 3 wherein the compound is a para disubstituted benzene.
5. The compound of any of claims 1, or 3-4 wherein R^6 is cyclized with the attached carbon atom at R_7 to form, including the fused benzene ring, a substituted tetrahydroisoquinoline ring.
6. The compound of any of claims 1, or 3-4 wherein X is nitrogen, and wherein R^7 and R^8 are cyclized to form, together with X, a pyrrolidine ring, and wherein R^9 is –CH2-N-pyrrolidinyl.
7. The compound of any of claims 1, or 3-6, selected from the group consisting of:

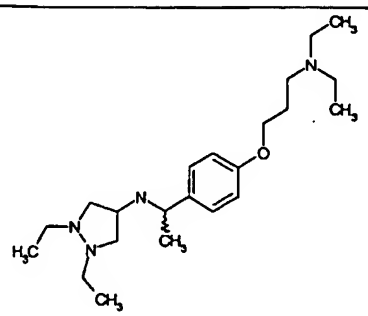
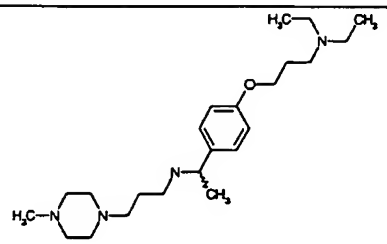
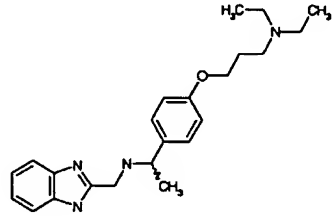
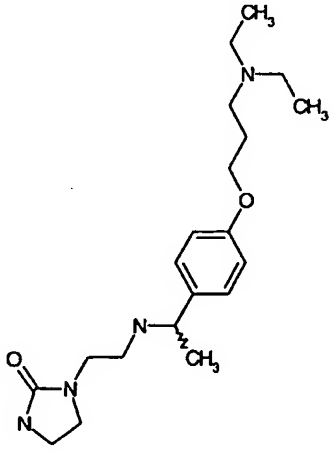
	Example Number	Structure		
	1			
	2			
	3			

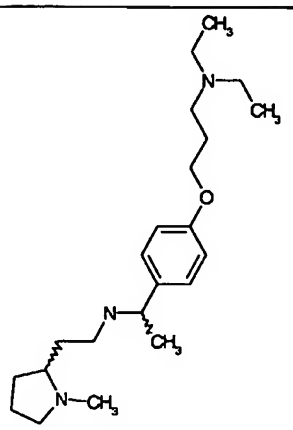
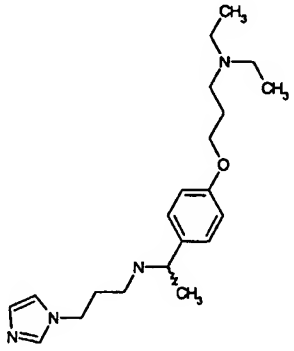
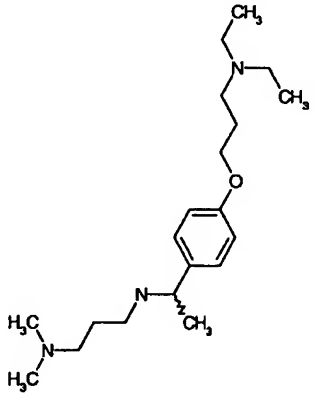
	4			
	5			
	6			
	7			
	8			

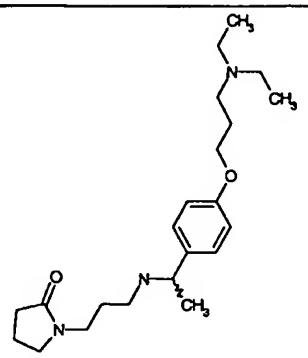
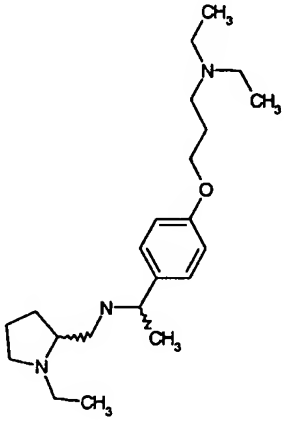
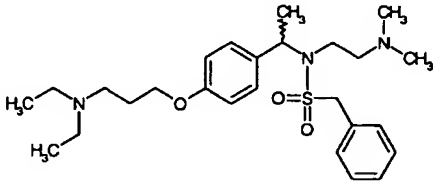
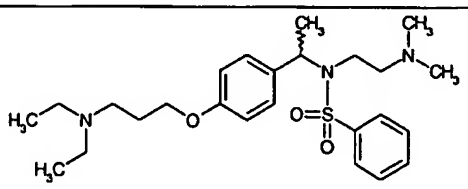
	9			
	10	 Chiral		
	11	 Chiral		
	12			
	13			
	14			

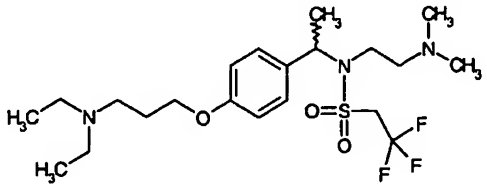
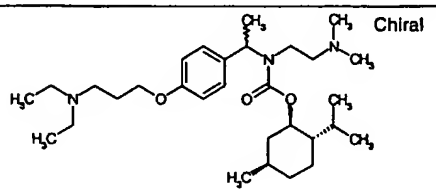
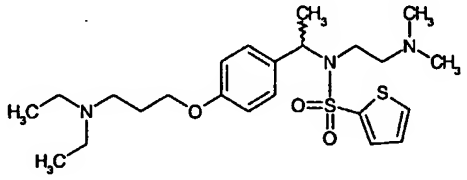
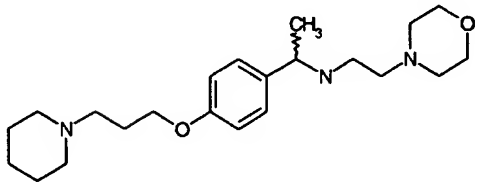
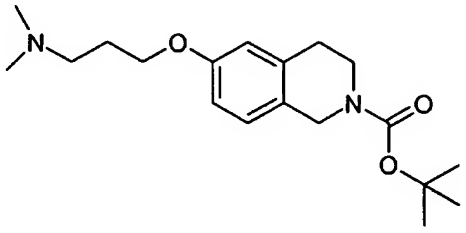
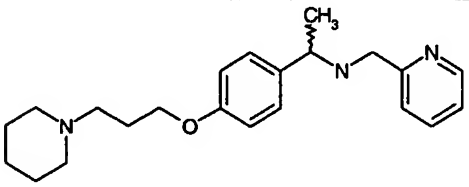
	15			
	16			

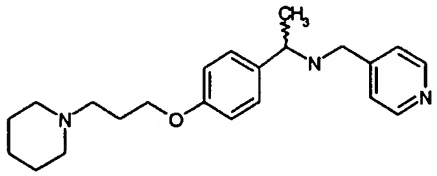
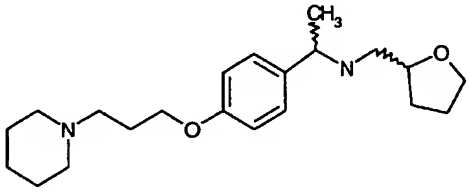
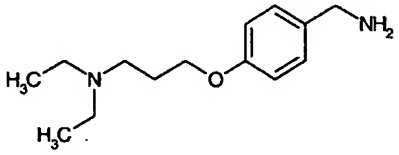
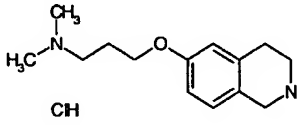
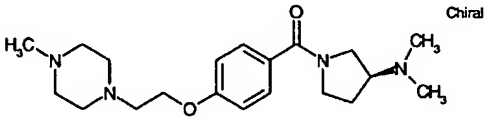
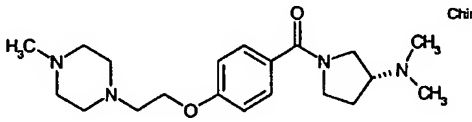
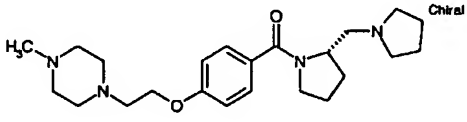
	17			
	18			
	19			

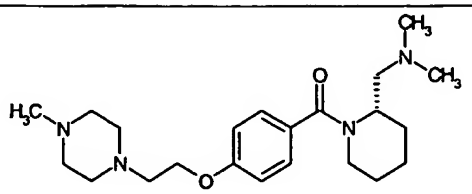
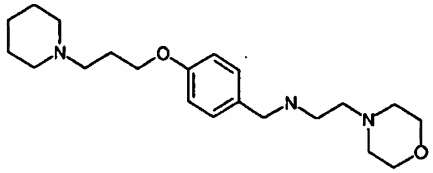
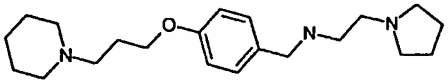
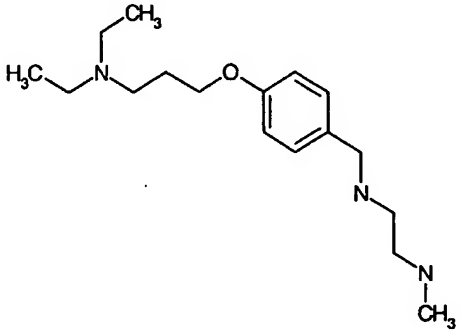
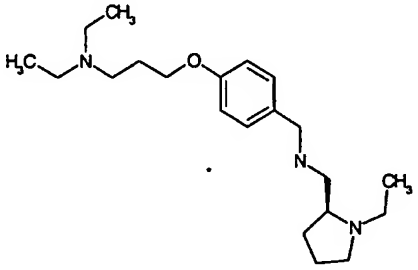
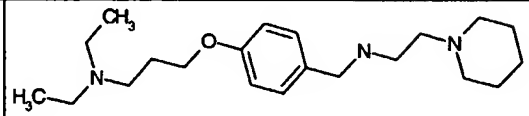
	20			
	21			
	22			
	23			

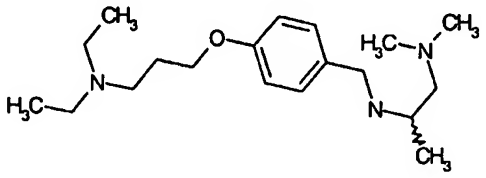
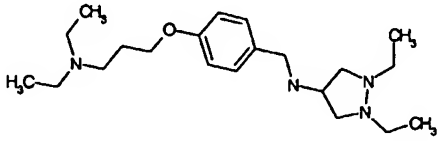
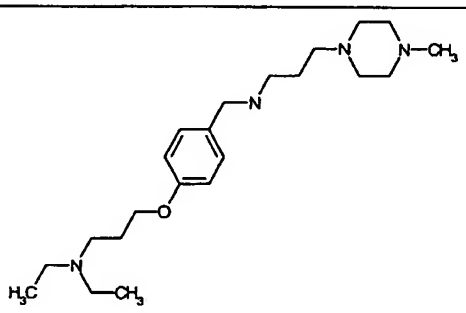
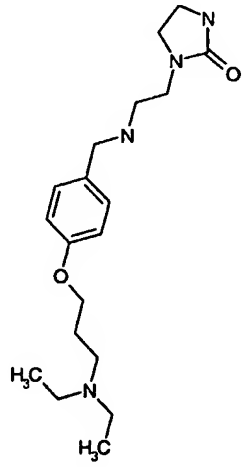
	24			
	25			
	26			

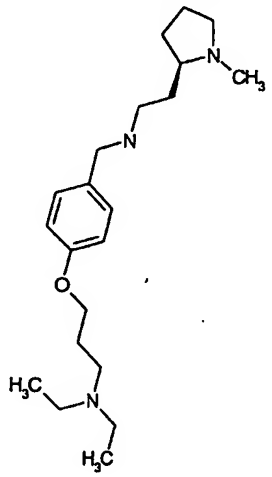
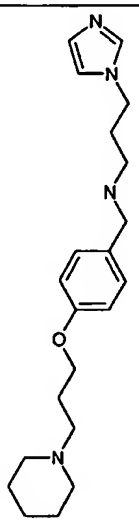
	27			
	28			
	29			
	30			

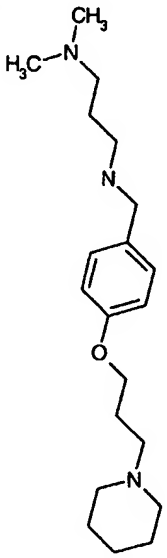
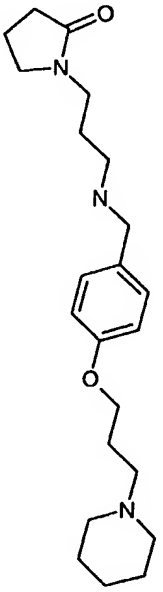
	31			
	32			
	33			
	34			
	35			
	36			

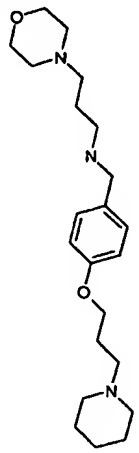
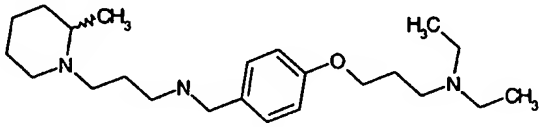
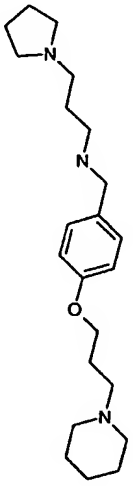
	37			
	38			
	39			
	40	 CIH CIH		
	41	 Chiral		
	42	 Chiral		
	43	 Chiral		

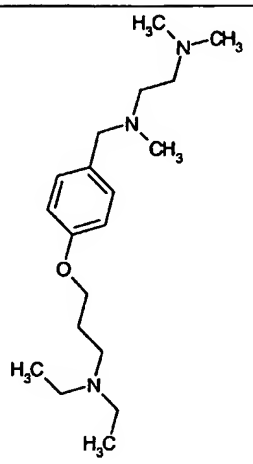
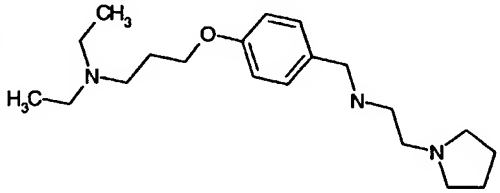
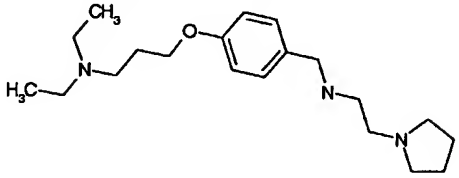
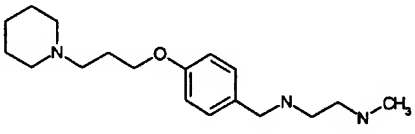
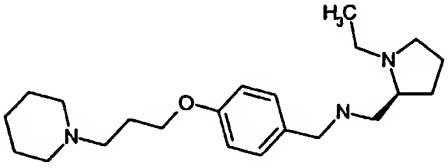
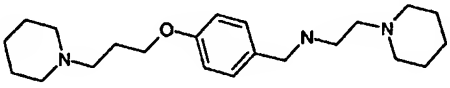
	44			
	45			
	46			
	47			
	48			
	49			

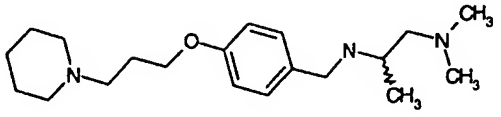
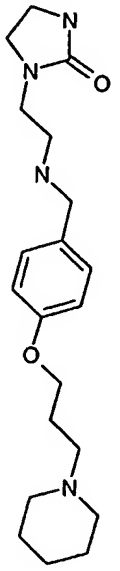
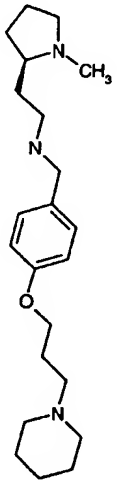
	50			
	51			
	52			
	53			

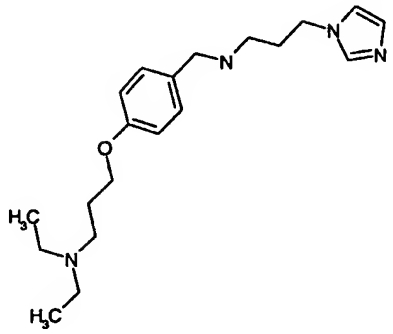
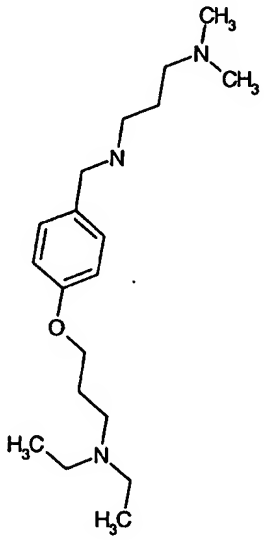
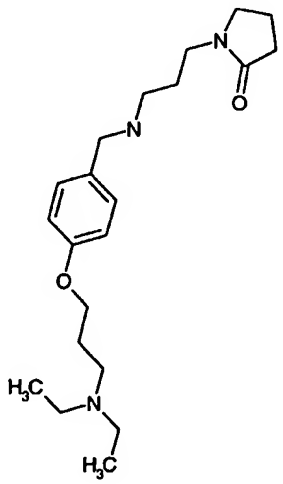
	54			
	55			

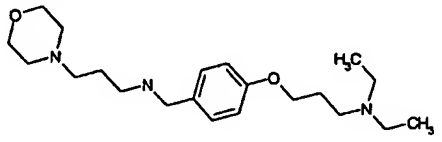
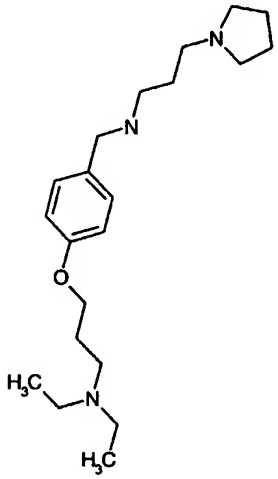
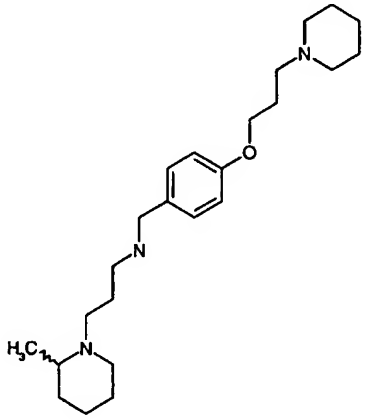
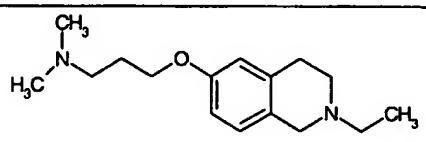
	56			
	57			

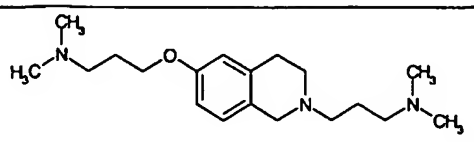
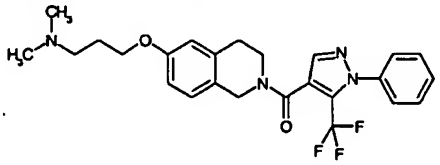
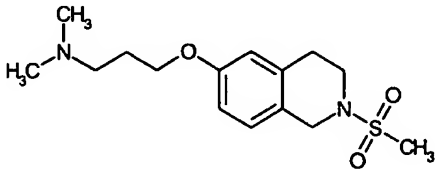
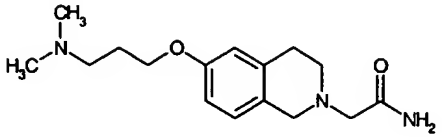
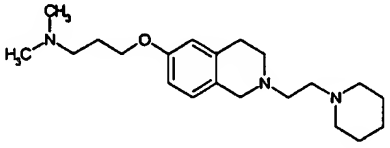
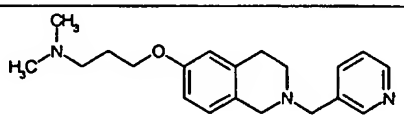
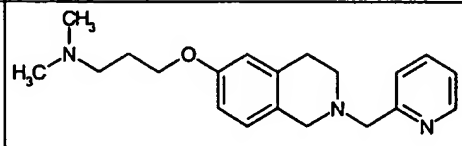
	58			
	59			
	60			

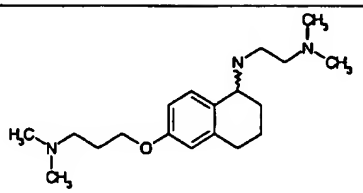
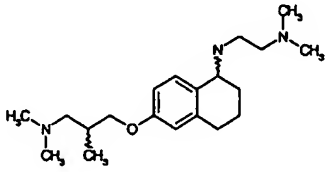
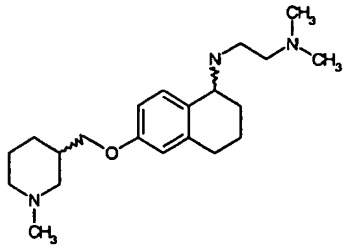
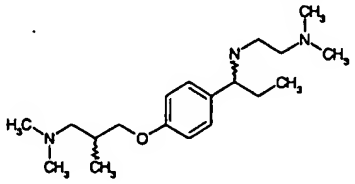
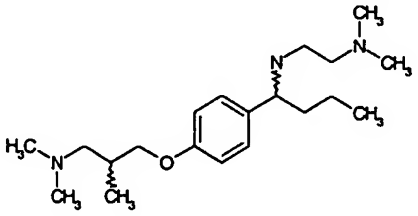
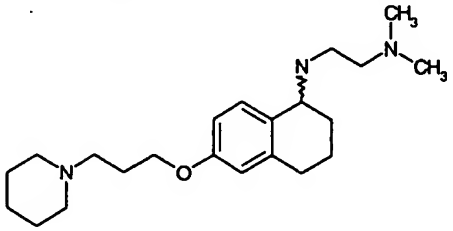
	61			
	62			
	63			
	64			
	65			
	66			

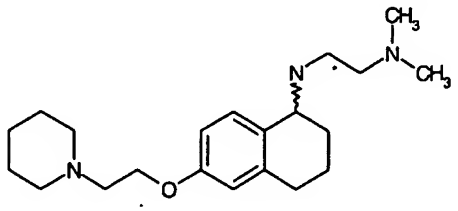
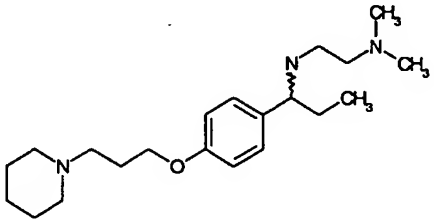
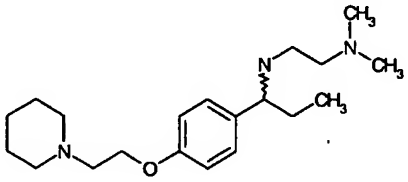
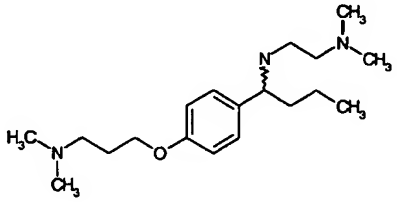
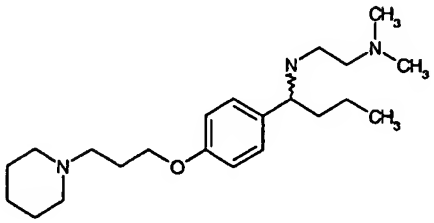
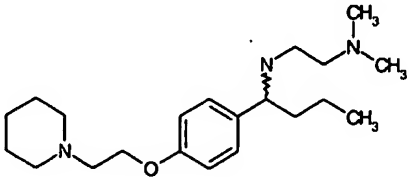
	67			
	68			
	69			

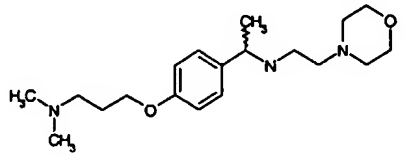
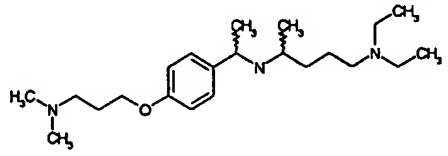
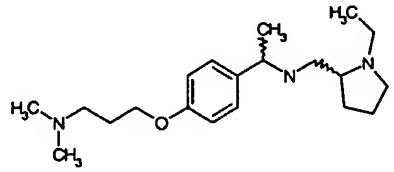
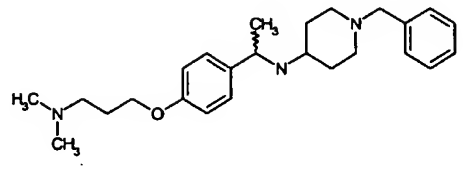
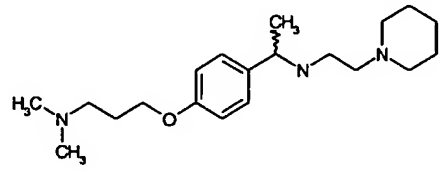
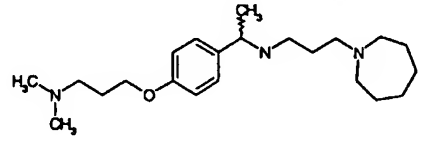
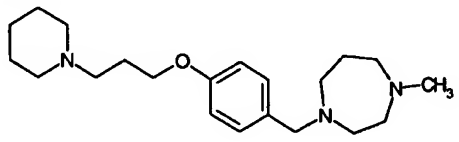
	70			
	71			
	72			

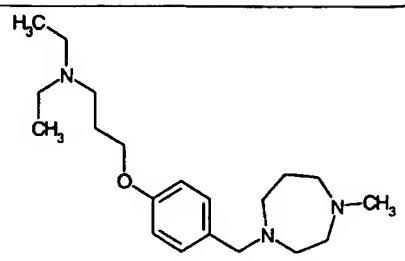
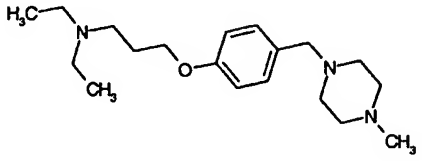
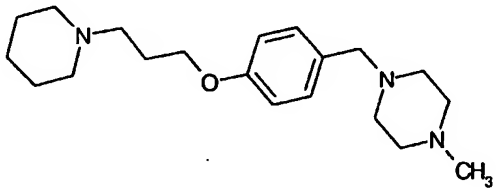
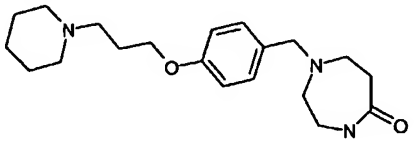
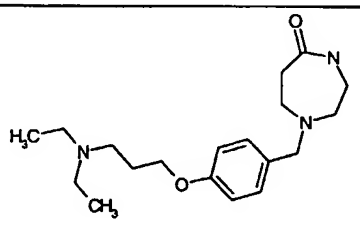
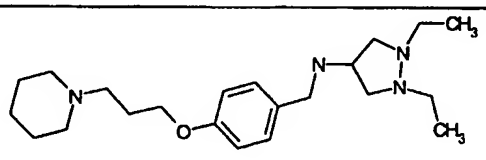
	73			
	74			
	75			
	76			

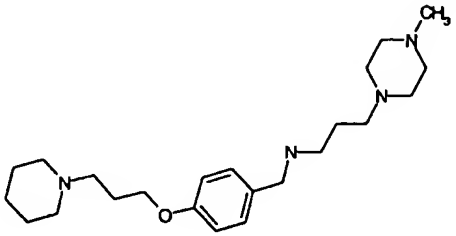
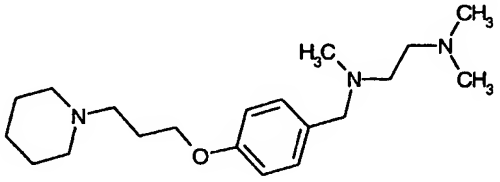
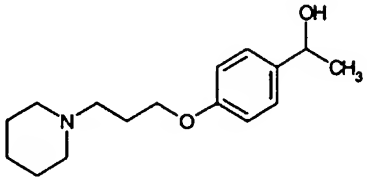
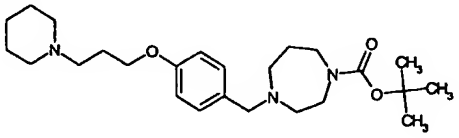
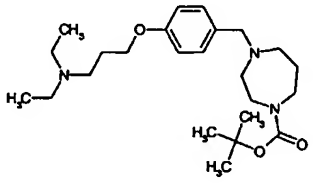
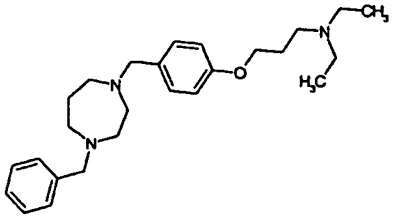
	77			
	78			
	79			
	80			
	81			
	82			
	83			

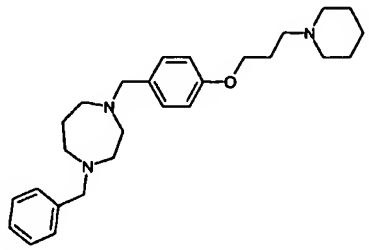
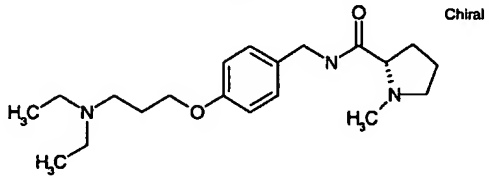
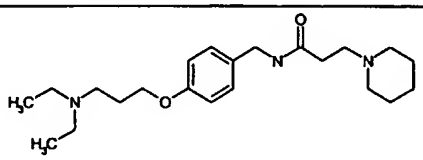
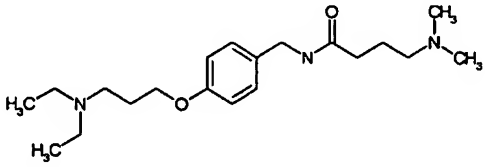
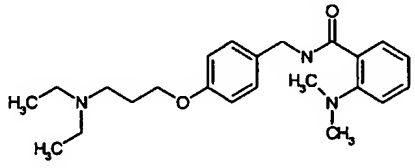
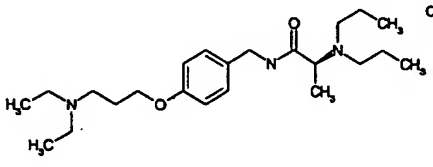
	84			
	85			
	86			
	87			
	88			
	89			

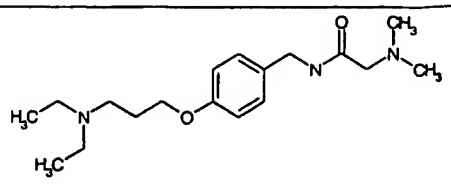
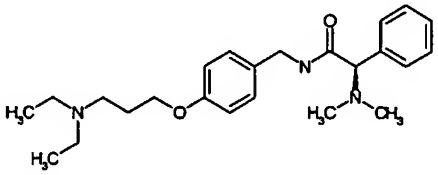
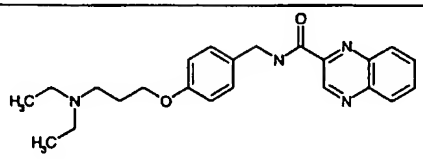
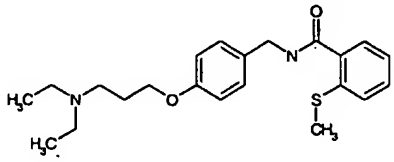
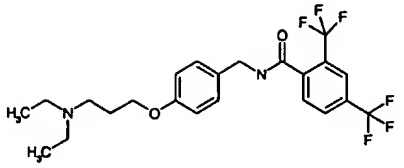
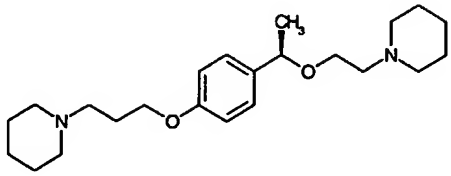
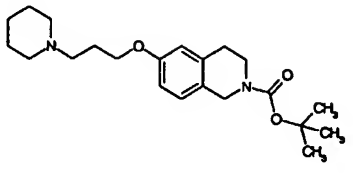
	90			
	91			
	92			
	93			
	94			
	95			

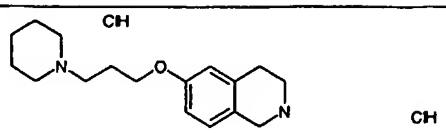
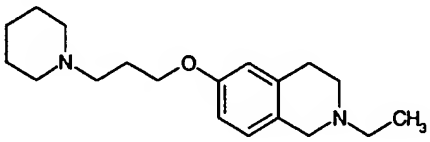
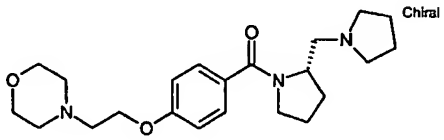
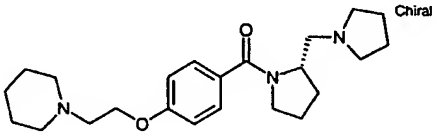
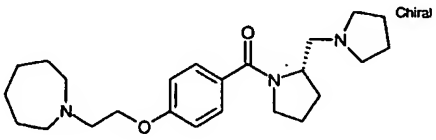
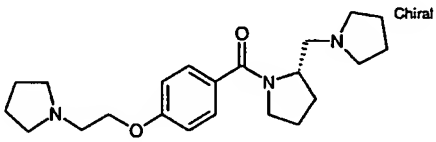
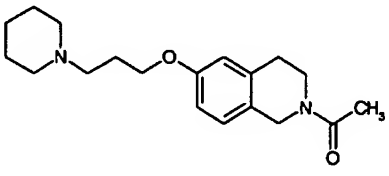
	96			
	97			
	98			
	99			
	100			
	101			
	102			

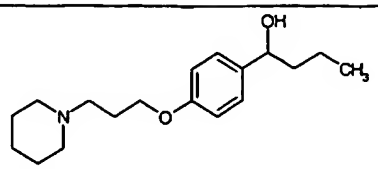
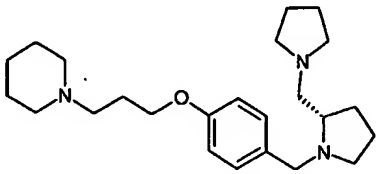
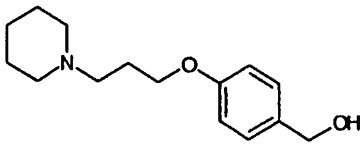
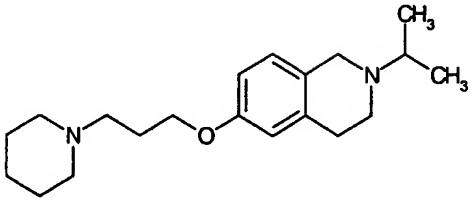
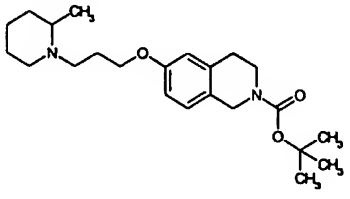
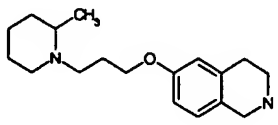
	103			
	104			
	105			
	106			
	107			
	108			

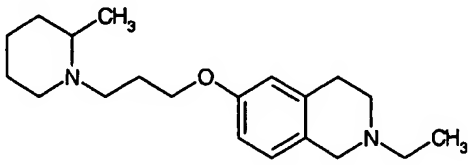
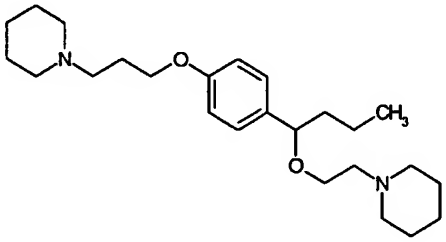
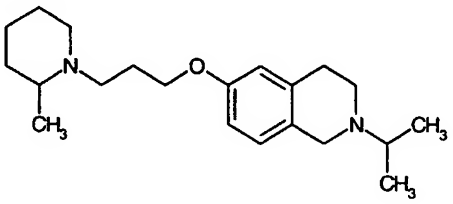
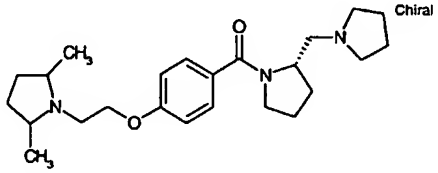
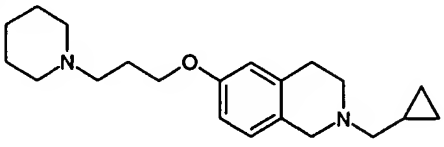
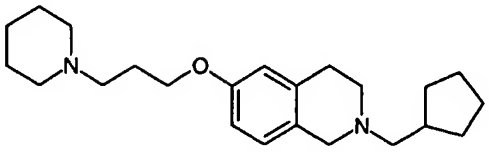
	109			
	110			
	111			
	112			
	113			
	114			

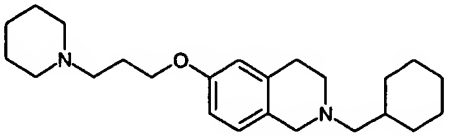
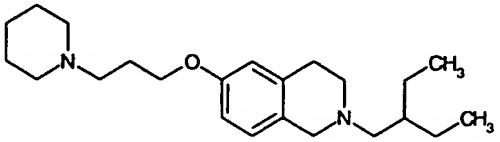
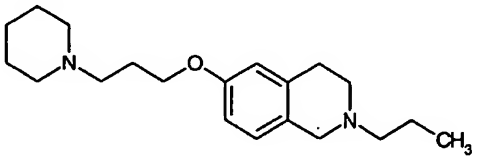
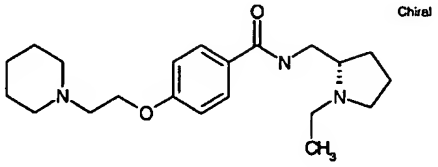
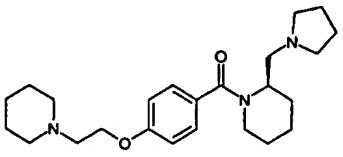
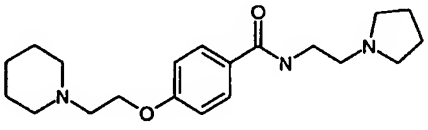
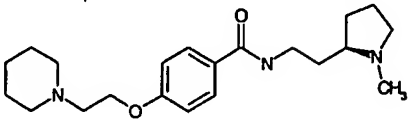
	115			
	116	 Chiral		
	117			
	118			
	119			
	120	 Chiral		

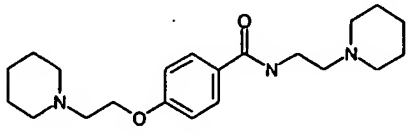
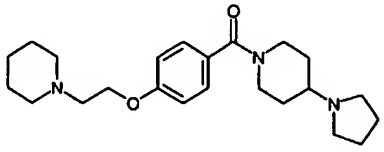
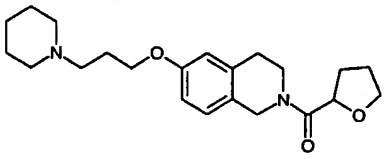
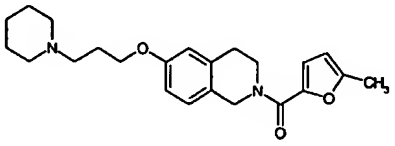
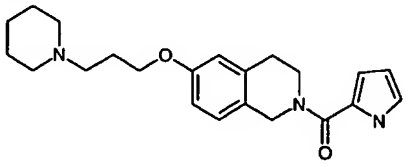
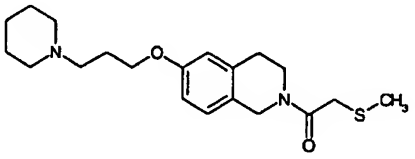
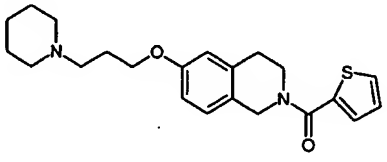
	121			
	122			
	123			
	124			
	125			
	126			
	127			

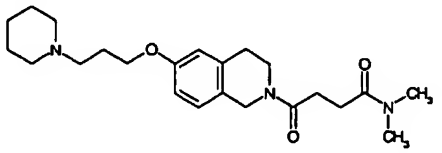
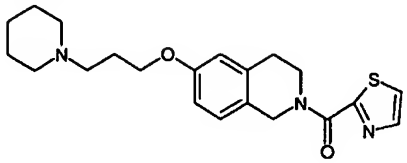
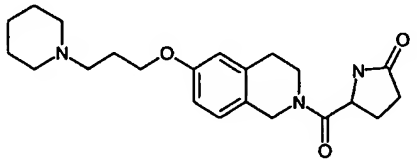
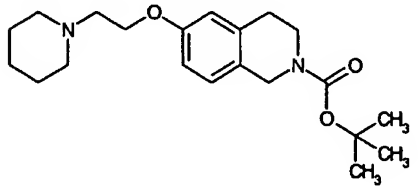
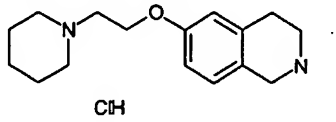
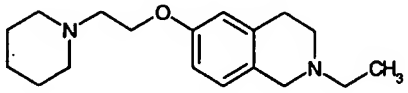
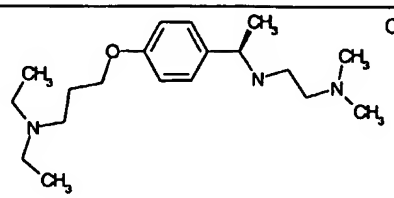
	128			
	129			
	130			
	131			
	132			
	133			
	134			

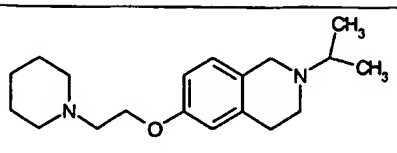
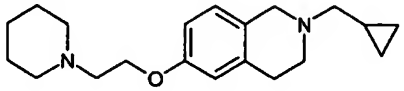
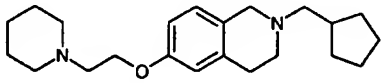
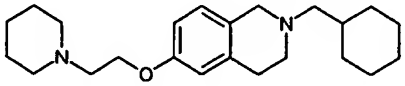
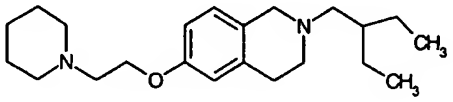
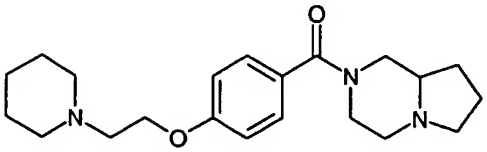
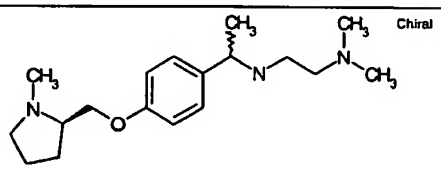
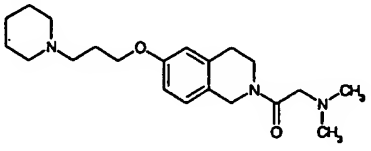
	135			
	136			
	137			
	138			
	139			
	140			

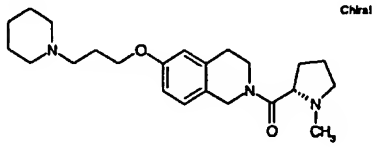
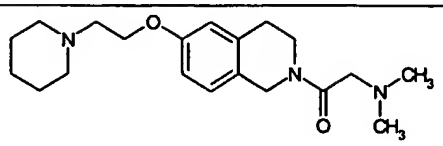
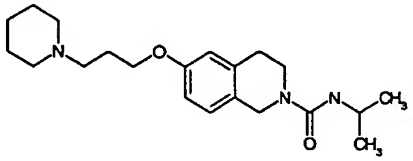
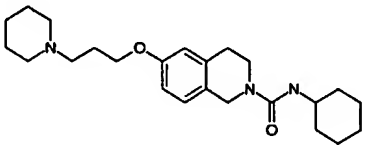
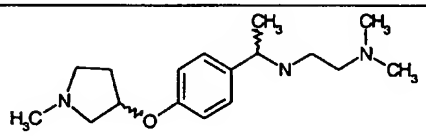
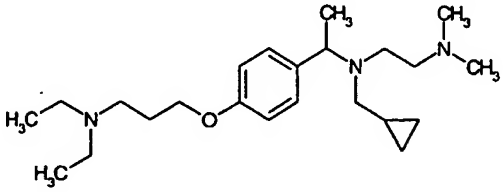
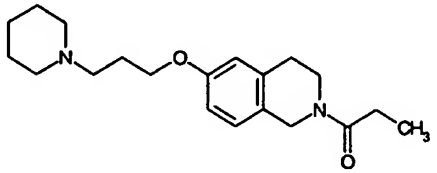
	141			
	142			
	143			
	144			
	145			
	146			

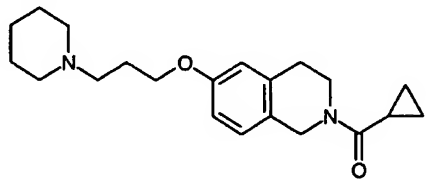
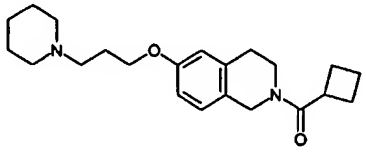
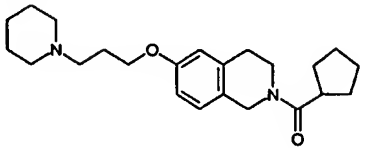
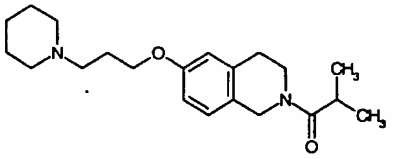
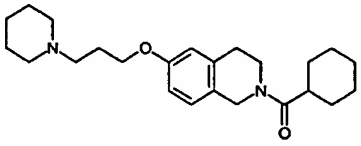
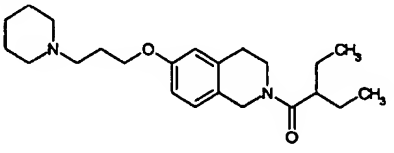
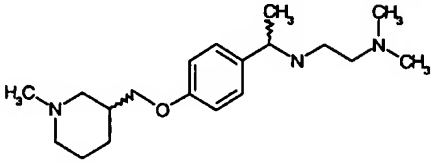
	147			
	148			
	149			
	150			
	151			
	152			
	153			

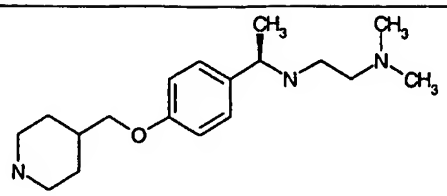
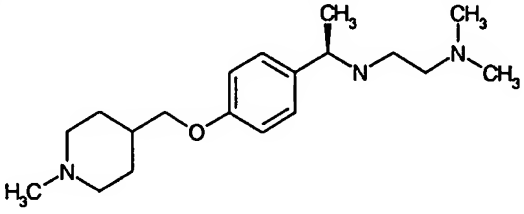
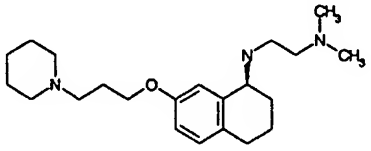
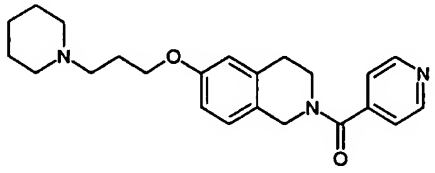
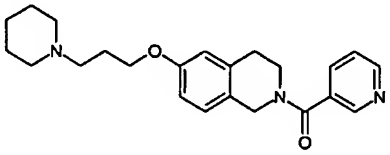
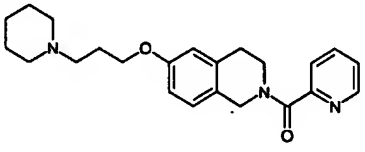
	154			
	155			
	156			
	157			
	158			
	159			
	160			

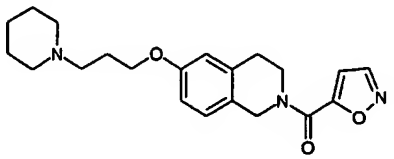
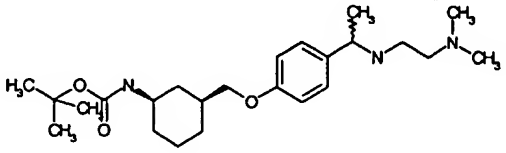
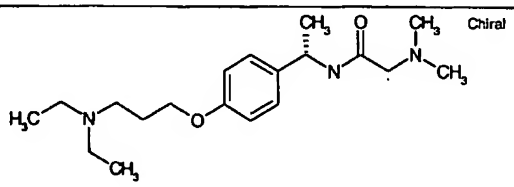
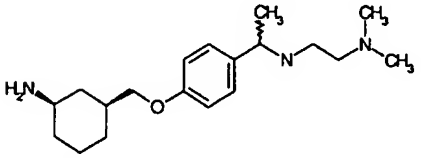
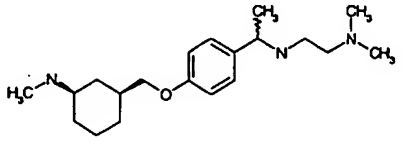
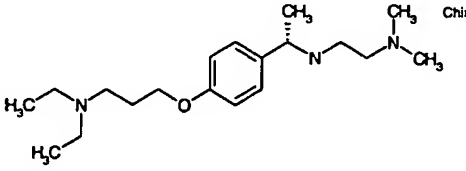
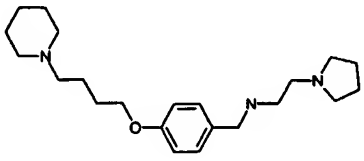
	161			
	162			
	163			
	164			
	165	 ClH ClH		
	166			
	167	 Chiral		

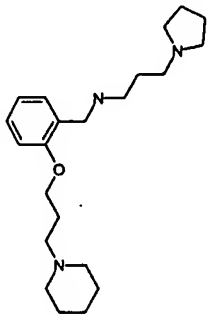
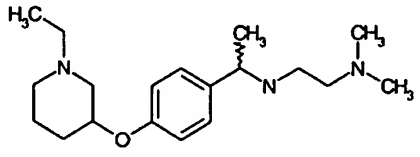
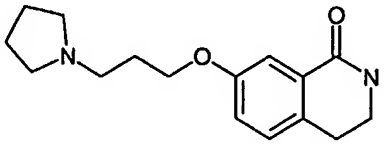
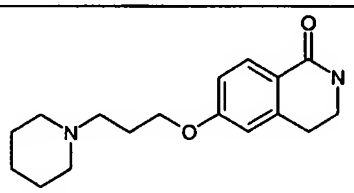
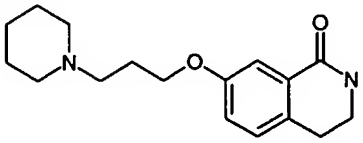
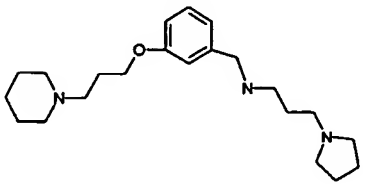
	168			
	169			
	170			
	171			
	172			
	173			
	174	 Chiral		
	175			

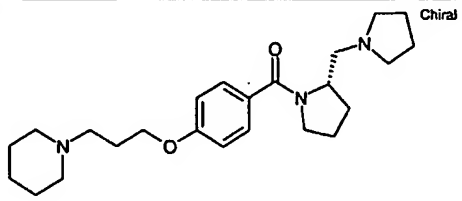
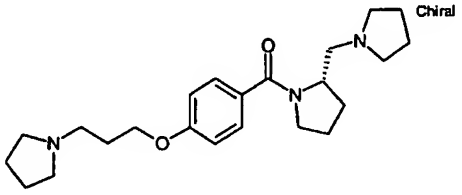
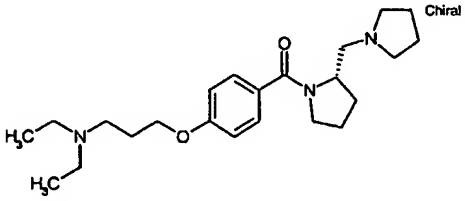
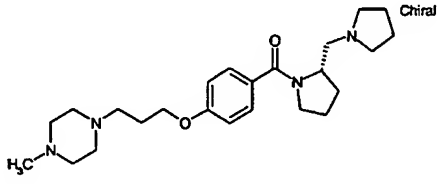
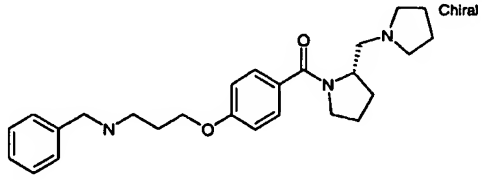
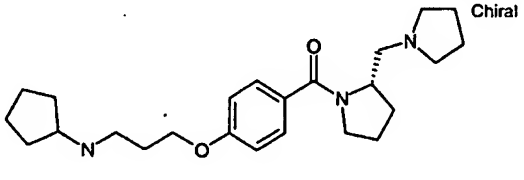
	176			
	177			
	178			
	179			
	180			
	181			
	182			

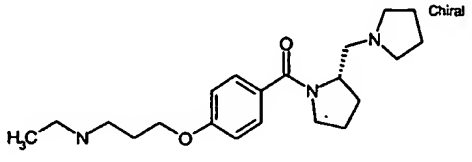
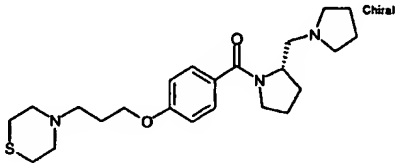
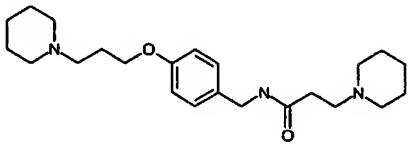
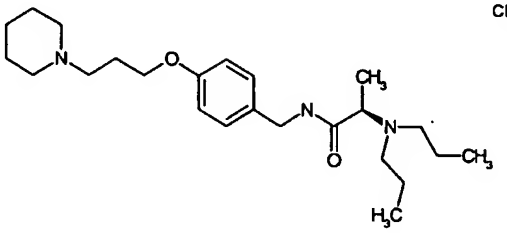
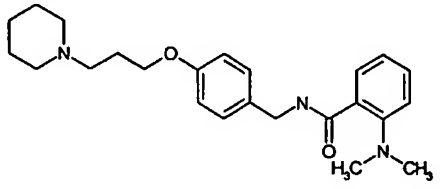
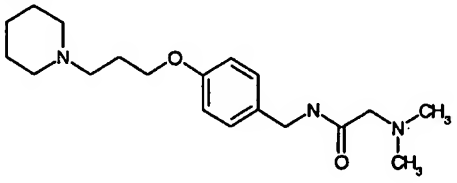
	183			
	184			
	185			
	186			
	187			
	188			
	189			

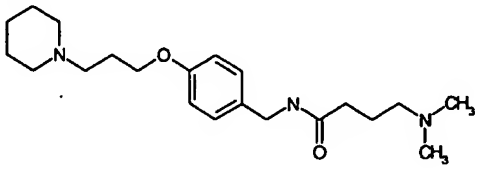
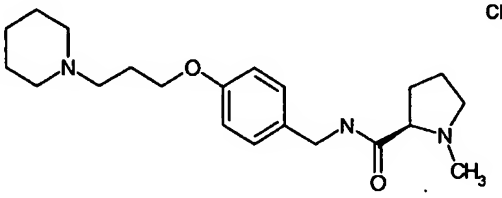
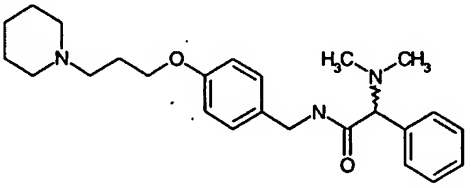
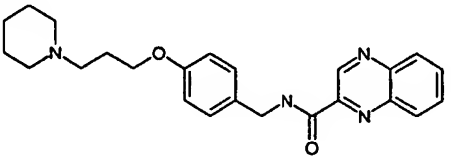
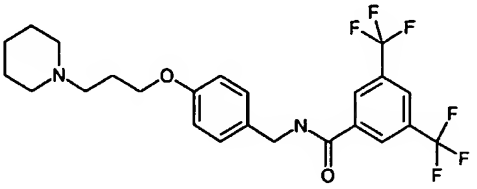
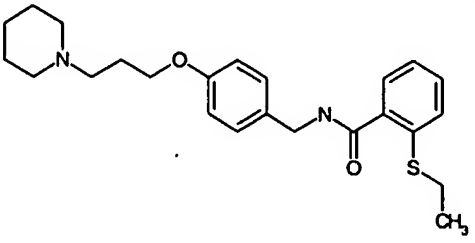
	190			
	191			
	192			
	193			
	194			
	195			

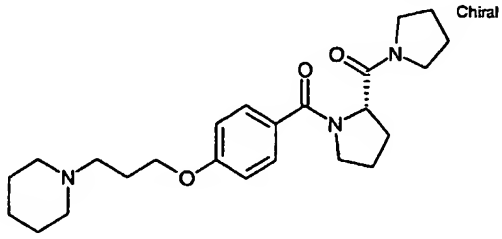
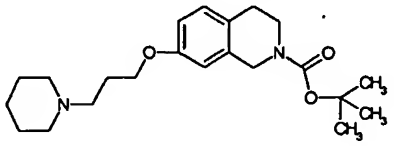
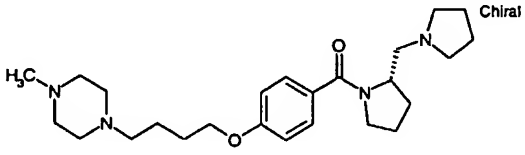
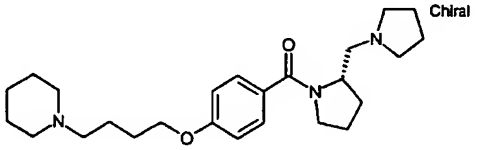
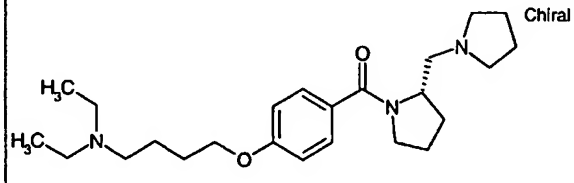
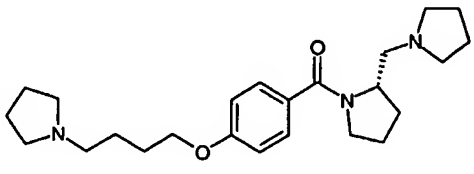
	196			
	197			
	198	 Chiral		
	199			
	200			
	201	 Chiral		
	202			

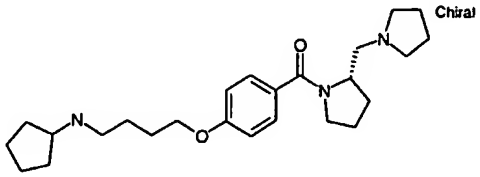
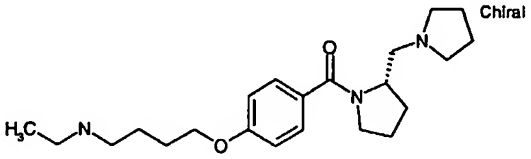
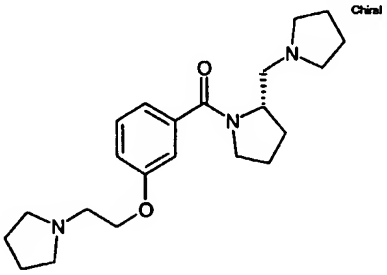
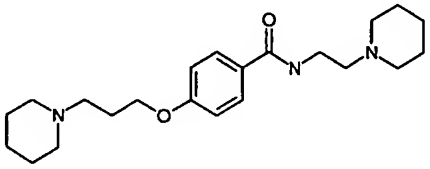
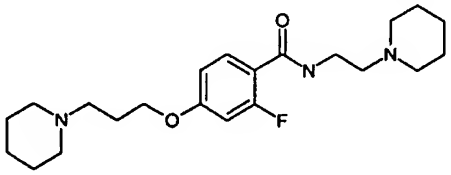
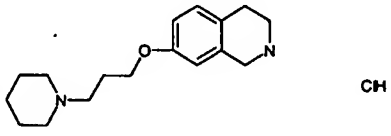
	203			
	204			
	205			
	206			
	207			
	208			

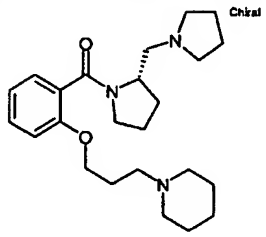
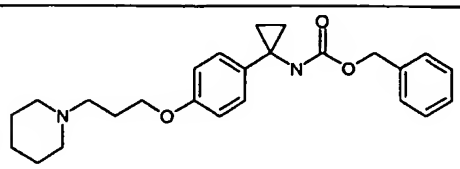
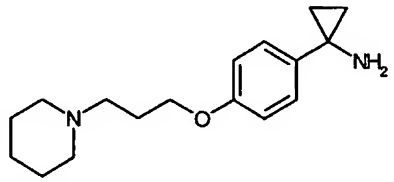
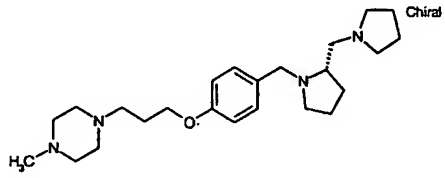
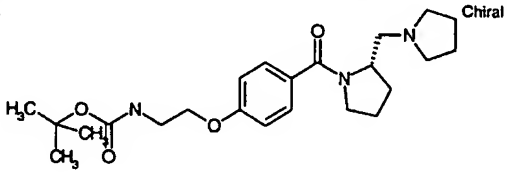
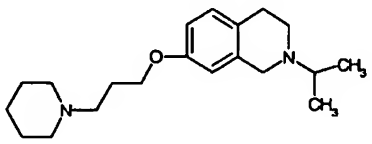
	209			
	210			
	211			
	212			
	213			
	214			

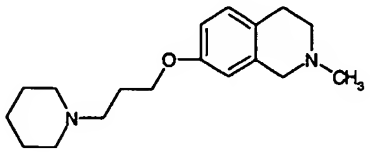
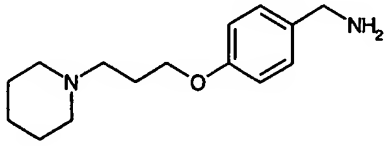
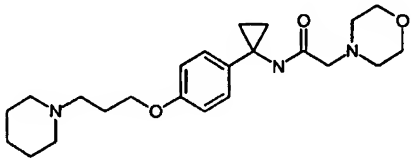
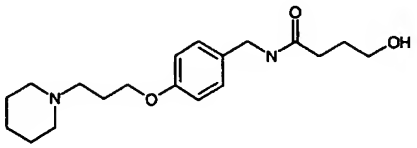
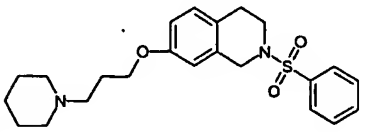
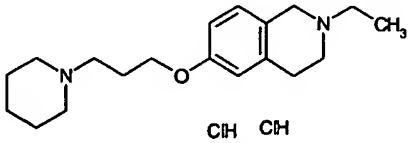
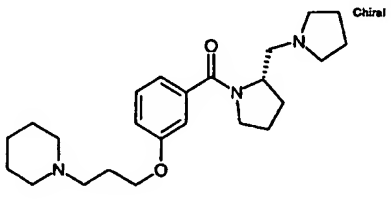
	215			
	216			
	217			
	218			
	219			
	220			

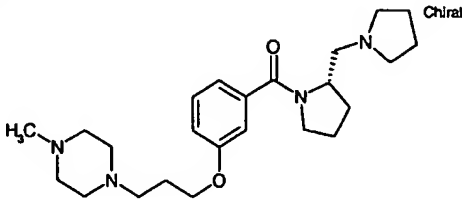
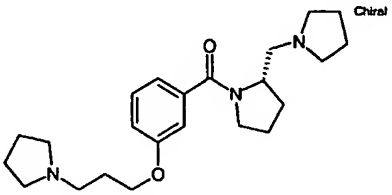
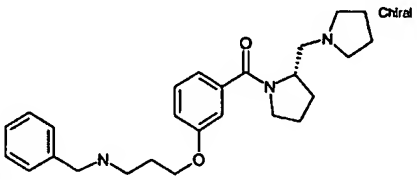
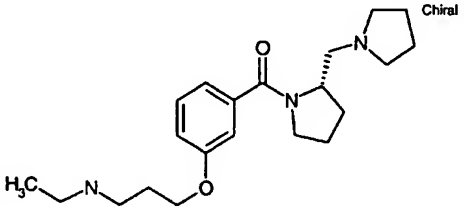
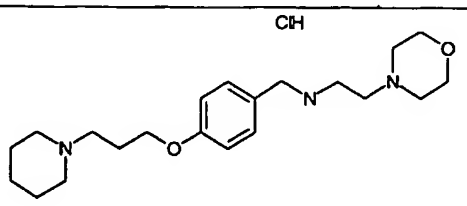
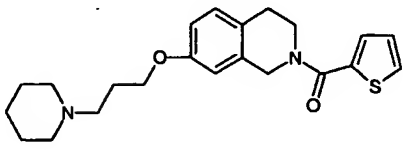
	221			
	222	Chiral 		
	223			
	224			
	225			
	226			

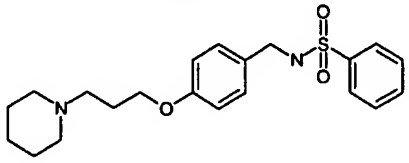
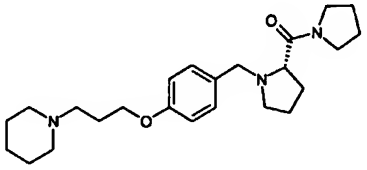
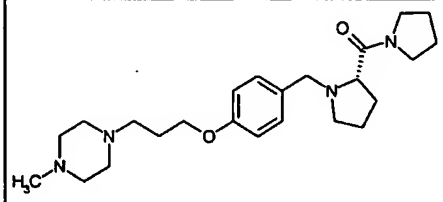
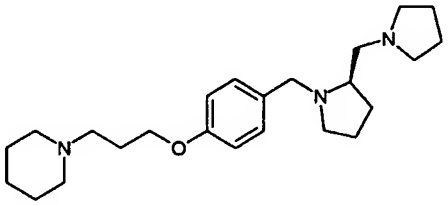
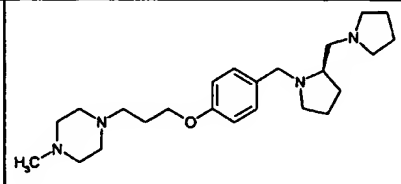
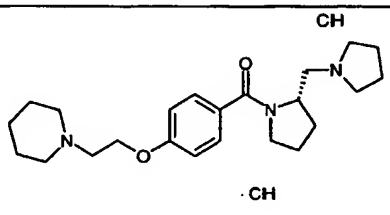
	227			
	228			
	229			
	230			
	231			
	232			

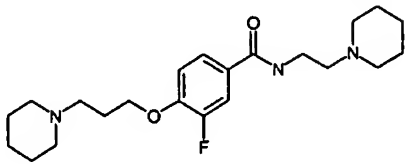
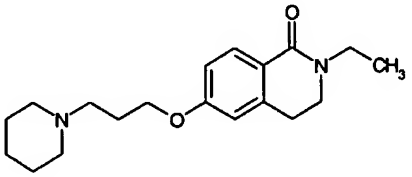
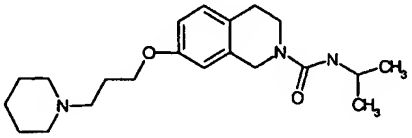
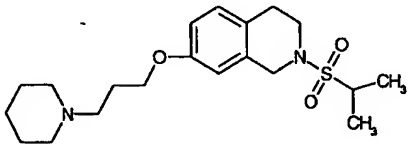
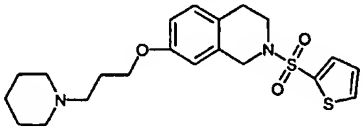
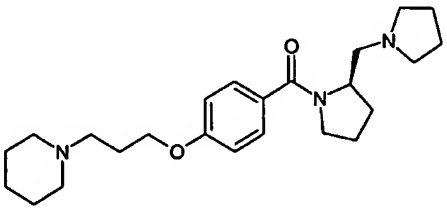
	233			
	234			
	235			
	236			
	237			
	238	 CH CH		

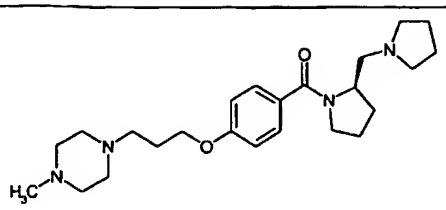
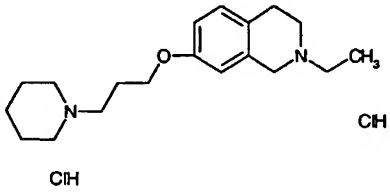
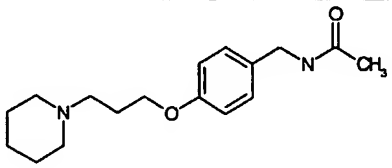
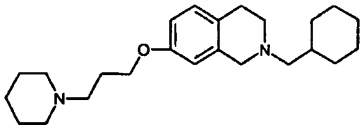
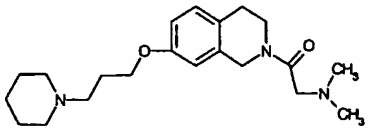
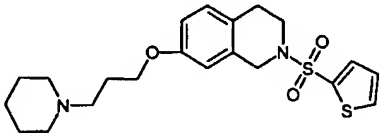
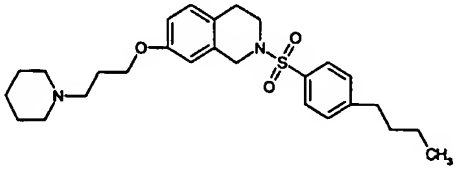
	239			
	240			
	241			
	242			
	243			
	244			

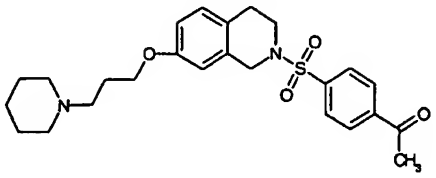
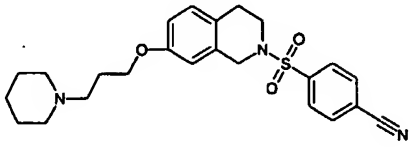
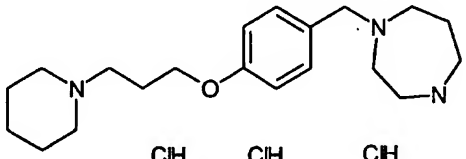
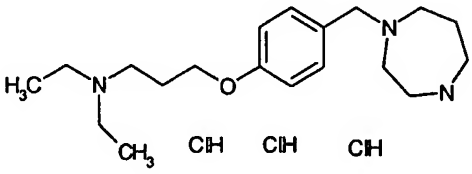
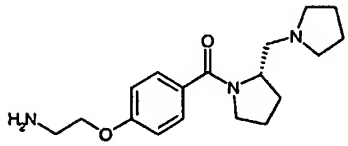
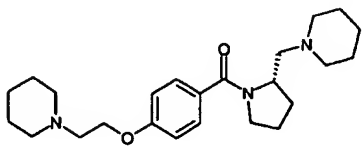
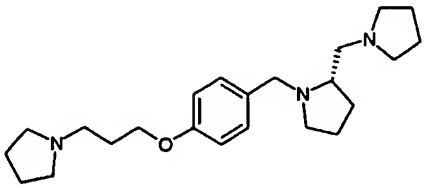
	245			
	246			
	247			
	248			
	249			
	250			
	251			

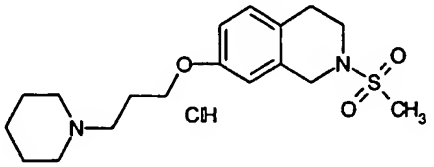
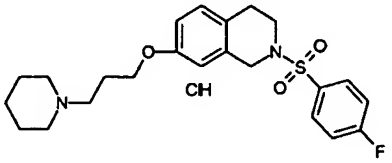
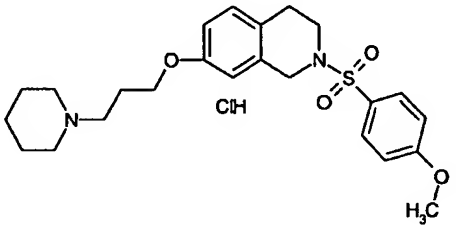
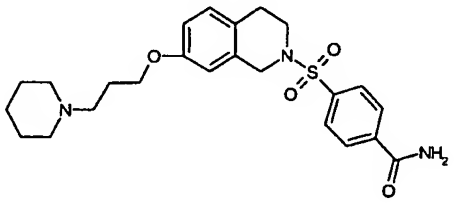
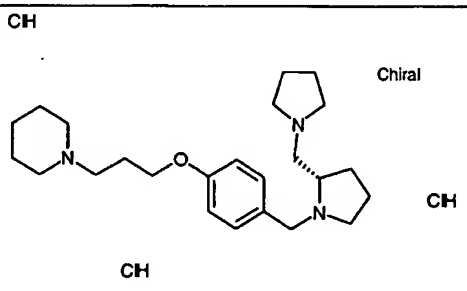
	252			
	253			
	254			
	255			
	256			
	257			

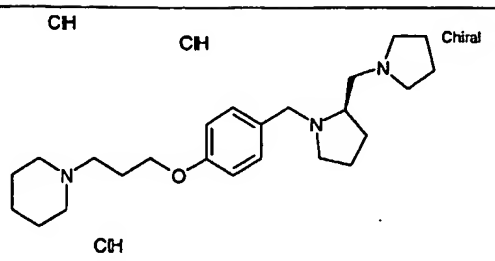
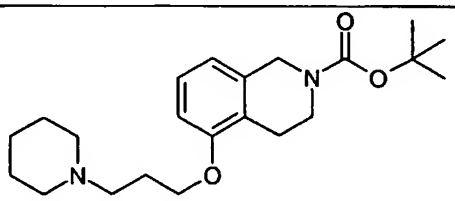
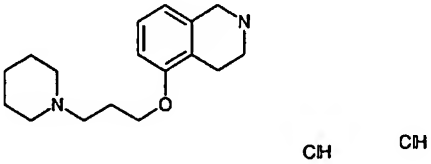
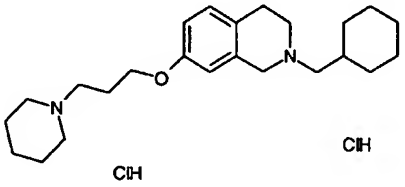
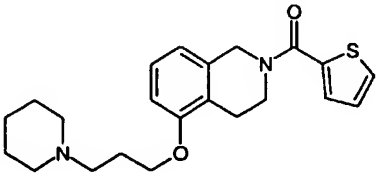
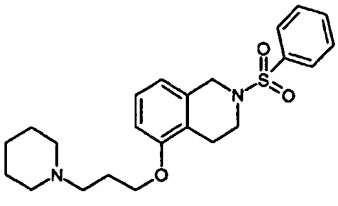
	258			
	259			
	260			
	261			
	262			
	263			

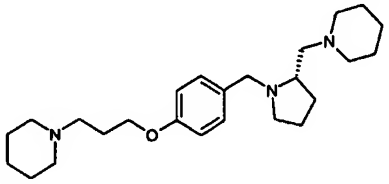
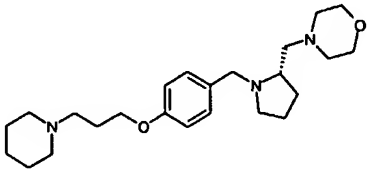
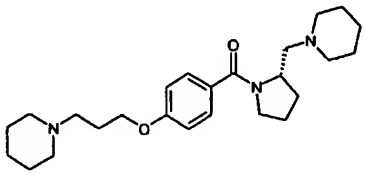
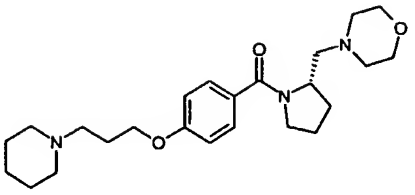
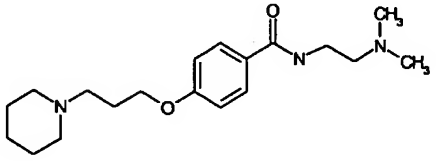
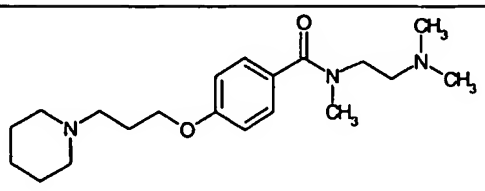
	264			
	265			
	266			
	267			
	268			
	269			

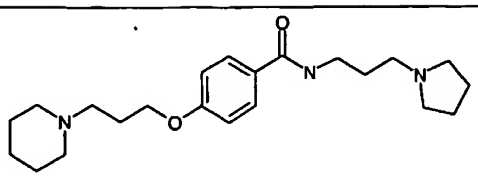
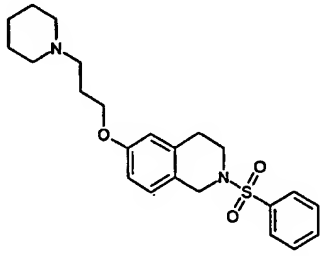
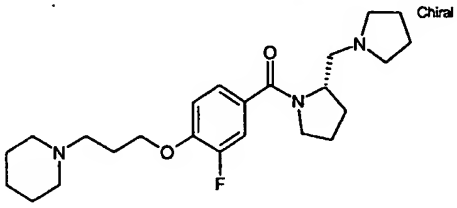
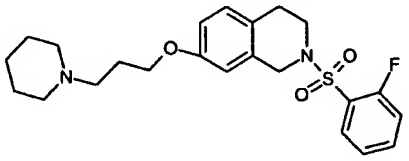
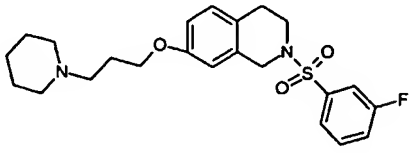
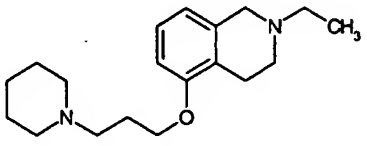
	270			
	271			
	272			
	273			
	274			
	275			
	276			

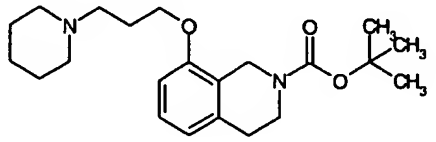
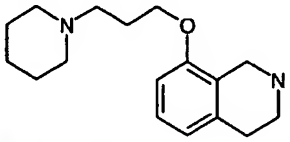
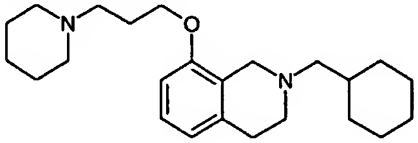
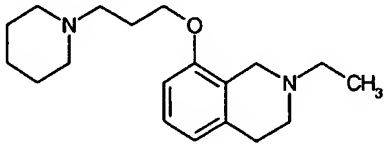
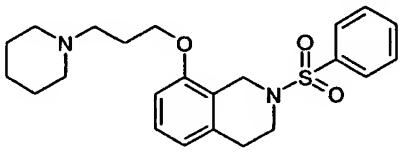
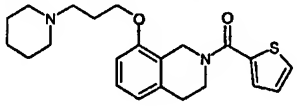
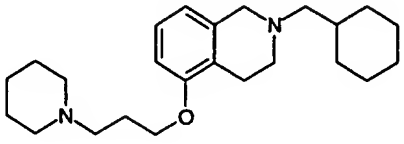
	277			
	278			
	279			
	280			
	281			
	282			
	283			

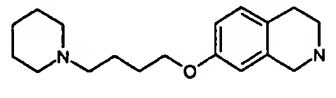
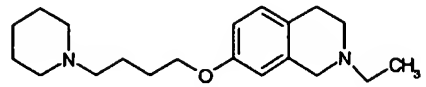
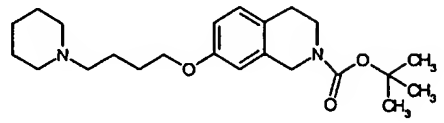
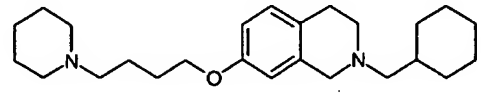
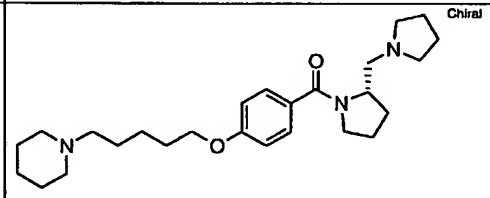
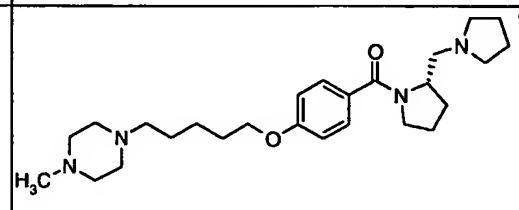
	284			
	285			
	286			
	287			
	288			

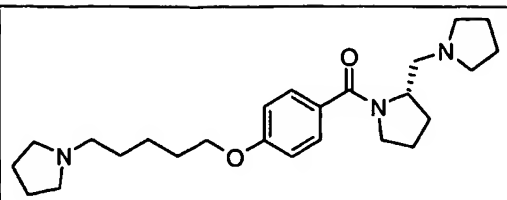
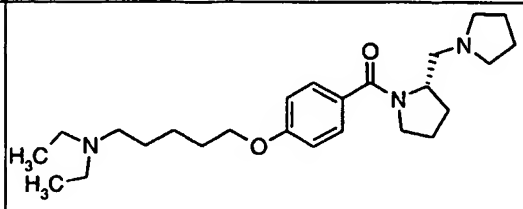
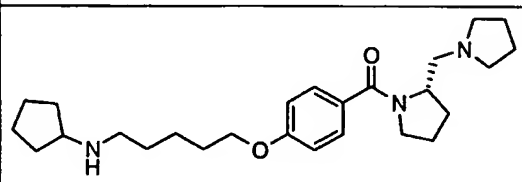
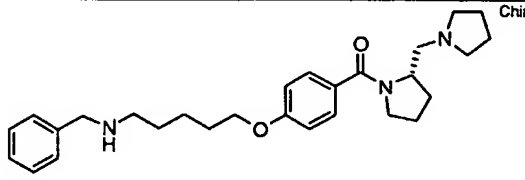
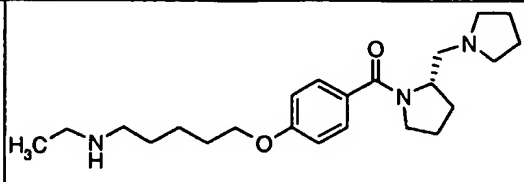
	289			
	290			
	291			
	292			
	293			
	294			

	295			
	296			
	297			
	298			
	299			
	300			

	301			
	302			
	303			
	304			
	305			
	306			

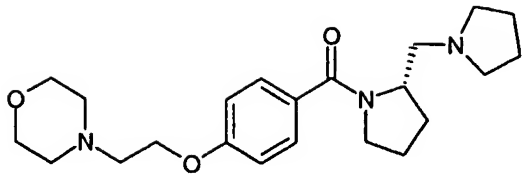
	307			
	308	 CH CH		
	309			
	310			
	311			
	312			
	313			

	314	 CH CH		
	315	 CH CH		
	316			
	317	 CH CH		
	318	 Chiral		
	319	 Chiral		

	320			
	321			
	322			
	323			
	324			

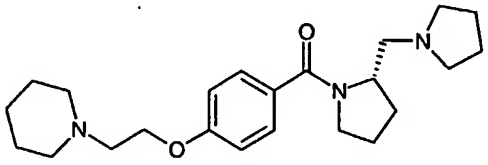
or a pharmaceutically acceptable salt or solvate thereof.

8. A compound of claim 1 wherein the compound has the structure:



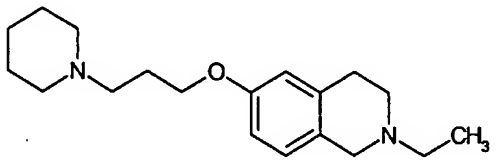
or a pharmaceutically acceptable salt or solvate thereof.

9. A compound of claim 1 wherein the compound has the structure:



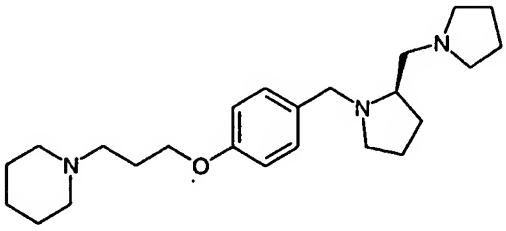
or a pharmaceutically acceptable salt or solvate thereof.

10. A compound of claim 1 wherein the compound has the structure:



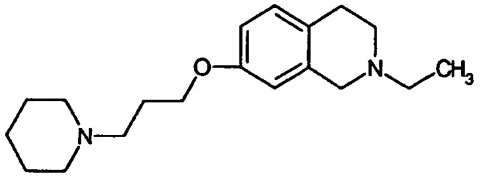
or a pharmaceutically acceptable salt or solvate thereof.

11. A compound of claim 1 wherein the compound has the structure:



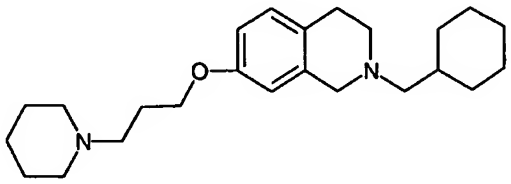
or a pharmaceutically acceptable salt or solvate thereof.

12. A compound of claim 1 wherein the compound has the structure:



or a pharmaceutically acceptable salt or solvate thereof.

13. A compound of claim 1 wherein the compound has the structure:



or a pharmaceutically acceptable salt or solvate thereof.

14. A pharmaceutical composition which comprises a compound of any of claims 1-14 and a pharmaceutically acceptable carrier.

15. A method of selectively increasing histamine levels in cells by contacting the cells with an antagonist of the histamine H3 receptor, said antagonists being a compound of any of claims 1-14.

16. A method of selectively increasing histamine levels in cells by contacting the cells with an antagonist of the histamine H3 receptor, said antagonists being a compound of Claim 2.

17. A method of selectively increasing histamine levels in cells by contacting the cells with an antagonist of the histamine H3 receptor, said antagonists being a compound of Claim 7.

18. A method of selectively increasing histamine levels in cells by contacting the cells with an antagonist of the histamine H3 receptor, said antagonists being a compound of Claim 9.

19. A method of selectively increasing histamine levels in cells by contacting the cells with an antagonist of the histamine H3 receptor, said antagonists being a compound of Claim 11.

20. The method of Claim 15 wherein the antagonist is characterized by having little or no binding affinity for the histamine receptor H4R.

21. A method for treatment or prevention of obesity which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of any of Claims 1-14.

22. A method for treatment or prevention of a disorder or disease in which inhibition of the histamine H3 receptor has a beneficial effect which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of any of claims 1-14.

23. A method for treatment or prevention of a disorder or disease in which inhibition of the histamine H3 receptor has a beneficial effect which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 2.

24. A method for treatment or prevention of a disorder or disease in which inhibition of the histamine H3 receptor has a beneficial effect which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 7.

25. A method for treatment or prevention of a disorder or disease in which inhibition of the histamine H3 receptor has a beneficial effect which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 9.

26. A method for treatment or prevention of a disorder or disease in which inhibition of the histamine H3 receptor has a beneficial effect which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 11.

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(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Patent Division, P. O. Box 6288, Indianapolis, IN 46206-6288 (US).

(72) Inventors; and

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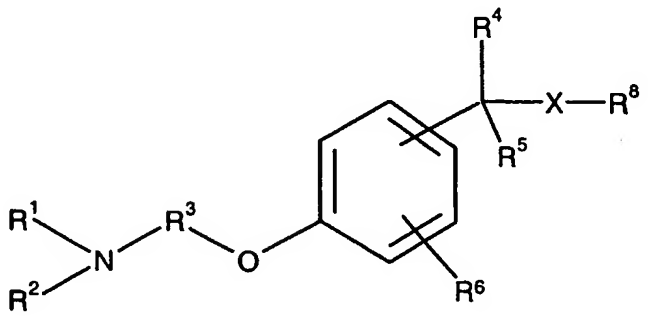
(74) Agents: **WOOD, Dan, L.** et al.; Eli Lilly And Company, P. O. Box 6288, Indianapolis, IN 46206-6288 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: NON-IMIDAZOLE ARYL ALKYLAMINES COMPOUNDS AS HISTAMINE H3 RECEPTOR ANTAGONISTS, PREPARATION AND THERAPEUTIC USES



(57) Abstract: The present invention discloses novel substituted aryl alkylamine compounds of Formula (I) or pharmaceutically acceptable salts thereofwhich have selective histamine-H3 receptor antagonist activity as well as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising such cyclic amines as well as methods of using them to treat obesity and other histamine H3 receptor -related diseases.

WO 02/076925 A3

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

(88) Date of publication of the international search report:
18 September 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/06644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C217/58 A61K31/395 A61K31/131 A61P3/00 A61P25/00
C07D295/08 C07D295/12 C07C217/20 C07C311/05 C07C311/13
C07C311/18 C07C237/08 C07D295/14 C07C217/74 C07C271/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 06254 A (SCHUNACK WALTER G ;SIGURD ELZ (DE); STARK HOLGER (DE); BIOPROJET S) 10 February 2000 (2000-02-10) claims 1,16,79-88 tab.1: no. 50,63,96,97,106 ---	1,4,14, 15,21,22
P,X	WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) claims 1,48-59; example 75 page 51, line 5 - line 16 ---	1,4,14, 15,21,22
E	WO 02 40456 A (BIOVITRUM AB ;NILSSON BJOERN (SE)) 23 May 2002 (2002-05-23) example 84 --- -/--	1,4,7

[X] Further documents are listed in the continuation of box C.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2003	16. 06. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Krische, D

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/06644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/62 C07C271/24 C07C233/73 C07C237/32 C07C311/17
C07D409/12 C07D207/16 C07D413/06 C07D471/04 C07D417/06
C07D409/06 C07D401/06 C07D307/46 C07D307/12 C07D241/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 11192 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 (1996-04-18) abstract; examples 78-103,110 ---	1,4,14
X	EP 0 114 410 A (RICHTER GEDEON VEGYESZET) 1 August 1984 (1984-08-01) claim 9; examples 1-7 ---	1,4,14
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International Application No
PCT/US 02/06644

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IPC 7 C07D243/08 C07D211/22 C07D217/08 C07D211/26 C07D207/09
C07D307/14 C07D213/38 C07D217/06 C07D215/20 C07D333/34
C07D207/26 C07D521/00 C07D233/36 C07D235/14 C07D231/04

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GILLIGAN ET AL: "Novel Piperidine sigma Receptor Ligands as Potential Antipsychotc Drugs" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 23, 1992, pages 4344-4361, XP002106858 ISSN: 0022-2623 abstract tab.1: cpd. 18e,g --- -/--	1,4,14

[X] Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/06644

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IPC 7 C07D207/14 //(C07D409/12,333:00,217:00),(C07D413/06,261:00, 217:00),(C07D471/04,241:00,209:00),(C07D417/06,277:00,217:00), (C07D409/06,333:00,217:00),(C07D401/06,217:00,207:00),

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 99 19293 A (AMERICAN HOME PROD) 22 April 1999 (1999-04-22) examples 4-7	1,4

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Krische, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/06644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D401/06,217:00,213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Krische, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/06644

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2,4,7,14-17,20-24 all in part

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,4,7,14-17,20-24 all in part

   Benzene compounds of general formulas I or II with R6 = hydrogen or halo and X = Oxygen, compositions and methods using these compounds.

2. Claims: 1-4,6,7,14-17,20-24 in part, 8,9,11,18,19,25,26

   Benzene compounds of general formulas I or II with R6 = hydrogen or halo and X = N or NR7, compositions and methods using these compounds.

3. Claims: 1,2,4,7,14-17,20-24 all in part

   Benzene compounds of general formulas I or II with R6 = hydrogen or halo and X = sulfur, compositions and methods using these compounds.

4. Claims: 1-3,6,7,14-17,20-24 all in part

   Carbobicyclic compounds of general formulas I or II with R6 cyclized with the attached carbon atom at the R5 position, compositions and methods using these compounds.

5. Claims: 1-3,6,7,14-17,20-24 in part, 5,10,12,13

   Tetrahydroisoquinoline compounds of general formulas I or II with R6 cyclized with the attached carbon atom at the R7 position; compositions and methods using these compounds.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search for invention 1 revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search for invention 1 has been restricted to the compounds of the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Information on patent family members

International Application No
PCT/US 02/06644

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0006254	A	10-02-2000	EP	0978512 A1	09-02-2000
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